IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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AVENTIS PHARMA, : Civil Action
SANOFI-AVENTIS U.S., LLC, :
:
Plaintiffs, :
:
v. :
:
HOSPIRA, INC., APOTEX,INC.,:
and APOTEX CORP., :
: 07-721-GMS
Defendants. : (Consolidated)

- - -

Wilmington, Delaware
Monday, October 26, 2009
9:00 a.m.
First Day of trial

- - -

BEFORE: HONORABLE GREGORY M. SLEET, Chief Judge

APPEARANCES:

STEVEN J. BALICK, ESQ.
Ashby & Geddes
-and-
GEORGE F. PAPPAS, ESQ.,
CHRISTOPHER N. SIPES, ESQ.,
MICHAEL N. KENNEDY, ESQ.,
MARK E. GELSINGER, ESQ.
Covington & Burling LLP
(Washington, D.C.)

Counsel for Plaintiffs

APPEARNCES CONTINUED:

MARY MATTERER, ESQ.
Morris James LLP
-and-
JAMES F. HURST, ESQ., and
IMRON T. ALY, ESQ.
Winston & Strawn LLP
(Chicago, IL)

Counsel for Defendant Hospira

DANIEL V. FOLT, ESQ.
Duane Morris, LLP
-and-
ARTHUR M. DRESNER, ESQ.,
RICHARD T. RUZICH, ESQ. (Chicago, IL),
KERRY B. McTIGUE, ESQ. (Washington, D.C.), and
IAN STEWART, ESQ.
(New York, N.Y.

Counsel for Apotex Defendants

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THE COURT: Good morning. Please be seated. Counsel, please take your seats.

Mr. Balick, do you want to begin?

MR. BALICK: Thank you, Your Honor. Good morning.

On behalf of the plaintiffs, from Covington & Burling we have George Pappas, Christopher Sipes, Kevin Collins. And at the table behind us Michael Kennedy and Mark Gelsinger. This gentleman doing the technical work is David Brooks, Your Honor.

THE COURT: He is one of the more important individuals in the room.

THE COURT: Ms. Matterer.

MS. MATTERER: Good morning, Your Honor. Mary Matterer from Morris James.

THE COURT: You can do it from there, if you would like.

MS. MATTERER: On behalf of Hospira this morning, I have with me James Hurst from Winston & Strawn, Mr. Imron Aly, and also from Hospira today we have the head of global intellectual property Jill Liu.

THE COURT: Counsel.

MR. FOLT: Good morning, Your Honor. Dan Folt from Duane Morris. It is my pleasure to introduce my partner Mr. Arthur Dresner, Kerry McTigue, Rick Ruzich and

Ian Scott.

THE COURT: Good morning.

(Counsel respond "Good morning.")

THE COURT: Are we ready to begin?

MR. HURST: Your Honor, one issue in advance. I am not sure we determined witness exclusion from opening statements. Are witnesses excluded from our opening statements? If so, I move they be excluded.

THE COURT: Have counsel discussed this?

MR. HURST: We haven't, Your Honor. I actually prefer it.

MR. PAPPAS: We don't mind if the witnesses all remain, but we have not discussed it before.

THE COURT: Would you like to discuss it for a moment or do you want me to just rule?

MR. DRESNER: I just want the experts to hear what's being said.

MR. HURST: I think, Your Honor, everybody but experts will be excluded.

THE COURT: That is, they will be excused.

MR. HURST: That's fine.

MR. PAPPAS: Could you give us a moment, Your Honor?

THE COURT: You may proceed, Mr. Pappas.

MR. PAPPAS: Thank you, Your Honor.

If I may, Your Honor, we have copies of some slides I intend to refer to in opening. Copies have been provided to the other side. In fact, all parties have exchanged slides and decided not to raise objections to the slides and just leave it to your discretion.

THE COURT: That is wonderful. If you could pass them to Ms. Walker, please.

MR. PAPPAS: Your Honor, I have one for you, for your law clerk, and for the courtroom deputy, and one for the court reporter.

May it please the Court...

As I understand, Your Honor, I will open for the plaintiffs, and we have talked with Mr. Hurst and Mr. Dresner. They each have openings on behalf of the defendants. I will try and be briefer than both of them put together.

Your Honor, we are here about a cancer drug.

The statistics in today's life are stark. What we know is that more than 500,000 men and women in the U.S. die from cancer each year, and, in fact, nearly one-half of all men and slightly over one-third of all women will develop cancer in their lifetimes.

In 1996 this trial is about Taxotere, a proven successful cancer formulation. Since its approval in the United States in 1996, it has generated gross revenues of

7.8 billion dollars. This formulation came about as the result of work of three inventors, Mr. Bastart, Dupechez and Fabre, Then Rhone-Poulenc and now Sanofi-Aventis, their work was recognized by the PTO when the '512 and '561 patents were issued. They are the two patents for you. Since its launch Taxotere has saved many lives.

Before today you have a challenge by two defendants, Hospira and Apotex. From our reading of the pretrial order and their briefs, they launch a multi-pronged attack. First they will tell you they don't infringe. Then they will tell you the patents are invalid. If those two fail, they will try inequitable conduct.

What I think is important for the Court to focus on from at least the plaintiffs' point of view, and we ask that you do, is that the defendants' case will largely take prior art out of context. And what we intend to do, in my opening and then in our presentation of the evidence, is to put all of the art and all of the events that took place in this search for this cancer formulation in context, so you can judge as you will.

We believe we will show you that their formulation, both Hospira's and Apotex's, infringe, that the patents are being attacked through hindsight analysis that the Federal Circuit warns against, and there is no basis for the inequitable conduct.

Your Honor, let's turn, if you will, to a discussion of Taxol. I do this, Your Honor, in order for you to understand Taxotere, which uses docetaxel that came later, we need to start with Taxol, the first taxane. I do that, Your Honor, for a very good reason. Not only will it give the Court historical context, but, most importantly, the '561 and the '512 patents describe the prior art, which was used Taxol used with Cremophor. And we found that polysorbate 80 worked better.

In order for you to judge in context not only the infringement allegations but the challenge to the prior art, it will assist the Court to understand the history of how Taxotere came to be.

We have prepared a timeline. While there are many events, we tried highlight the most important ones.

What you will hear, and I think will be convinced of by the end of the trial, Your Honor, is Taxol and Taxotere come from a class of drug called taxanes. They are tough to deal with. They are insoluble in water, and they have vexed scientists since they were discovered.

The story begins with the discovery of molecules of paclitaxel, which became Taxol.

In 1963, it was discovered by Wall and Wani at the Research Institute in North Carolina that they had isolated paclitaxel from the back of the Pacific Yew tree.

In the 1970s Wall and his coworkers discovered that paclitaxel had unique mechanisms of action. Basically, Your Honor, they interfere with the growth of cells. Cancer cells -- this is the real tragedy of the disease -- grow immensely faster than our good cells, so they are replicated every day, overtake the battle against the good cells, and eventually, unfortunately, many of our citizens die.

What they found about the taxanes, specifically paclitaxel and docetaxel, Taxotere that we are here about, once into the cell, it interferes with the mechanism of cell division and stops and arrests the cell's rapid multiplication, and ultimately, in many patients, that cancer cell dies.

It is a fundamental explanation, Your Honor, but it is one that I have been able to understand and explains basically why these drugs ended up being so important. But they are tough to deal with.

In any event, in 1971, the researchers isolated paclitaxel as an active compound and published an article describing it.

In 1977, the National Cancer Institute selected paclitaxel for clinical development, it did, indeed, look to be such a project drug. It showed promising anticancer activity and work began to formulate this drug.

But as I mentioned, Your Honor, this is a tough

drug to work with. Let me tell you why. They found that these taxanes have low solubility in water. They won't dissolve in water. What formulators will tell you is as soon as they run into a new molecule that won't dissolve in water, that spells trouble, because you have to get it into water.

The only way Taxol, paclitaxel and docetaxel, can be administered to a human being is in solution, in an I.V. bag, through a perfusion into the vein. You can't take it orally. You can't take an enema. It's got to go through the bag into the vein.

So the first challenge is, they have to be able to get this molecule into solution or you don't even get out of the starting blocks, it won't work.

Now, it took years to find an answer. And ultimately what they found -- this was the National Cancer Institute, then soon working with Bristol-Myers Squibb, is if they used a surfactant called Cremophor, about which you will hear much, Your Honor, and ethanol in a perfusion, they could get paclitaxel into solution.

They did so, and clinical trials began in 1983. Almost immediately they were halted, because a patient died. And many patients experienced anaphylaxis, the most severe form of hypersensitivity reaction. Hopefully something no one in this courtroom will ever get. But, Your Honor, if it

hits, it hits hard and it hits fast. Doctors and nurses are trained to recognize it. They know the symptoms and they know what they have to do. They have to administer antihistamines. They have to bring your heart rate down. Otherwise, your veins and your throat constricts, and you will die.

Doctors and nurses who know what they are doing -- you will hear from our side -- know about anaphylaxis. There is no trouble recognizing it. But you better get it and get it faster or the patient dies.

Well, in 1984 those life-threatening anaphylactics halted clinical trials, and the future of Taxol was in doubt.

You might ask yourself, is this going to be an obviousness attack here? And the case basically boils down, from the defendants' point of view, to this. Cremophor was a good molecule and polysorbate 80 was a surfactant. It should have been substituted. So why are we here? That was obvious.

I want you to ask yourself this question, Your Honor: Polysorbate 80 was known about in 1984. You could get it off the shelf. It was a known surfactant. It had been developed. Yet in 1984, when the trials were stopped due to death and severe anaphylaxis, Bristol-Myers Squibb and the National Cancer Institute looked for another answer.

They didn't pick polysorbate 80. It's available. In fact, prior 1984, the National Cancer Institute and Bristol-Myers Squibb had a drug called etoposide, another drug you will hear a lot about, a cancer drug. It used polysorbate 80. But they didn't pick it. Well, the answer is they didn't pick it because they didn't think it would work.

And so what happened was the Taxol trials you ultimately went forward, Your Honor, but what they had to do with Taxol to protect against the anaphylaxis was they slowed the infusion way down initially to 24 hours. Yes, you had to check into a hospital, lie in a bed, get hooked up and have a needle in your vein for 24 hours. That's how they had to slow the infusion down. It was eventually brought down to three hours, but they had to slow it down.

And to guard against anaphylaxis, they had to give the patient for 45 minutes to an hour, intravenously prior to the administration a combination of corticosteroids and antihistamines. And even then, the nurses had to monitor, beside your bed, if you got Taxol, was what is called, even today, a shock cart. It's with you, always, with Taxol. And that is a shock cart that has on it the paddles to bring your heart back and epinephrine and other drugs.

Now, the conventional wisdom, Your Honor, even

though the trials started, it was well known that they needed to find a substitute for Cremophor. You will hear of many efforts that were tried. They all failed. They either were not stable enough, too toxic or not effective. As you can see, Your Honor, in 1985, on our time line, there are ongoing efforts to development Cremophor free formulation of Taxol.

Yalkowsky, a truly famous man in this field, tried two different formulations. He failed. And he was trying things like pluronic L64 and emulsions. Again, if PS 80, polysorbate 80, was so obvious, why were some of the finest minds in the world trying to find a substitute for Cremophor and nobody used polysorbate 80. And the belief was, Your Honor, that it was, there wasn't a suitable formulation.

In the hypersensitivity reactions written by Weiss and others, some of the most famous men, including Von Hoff in the field of formulation, wrote in 1990, if Cremophor is a suspected initiator of reactions from Taxol, could some substitute excipient be used to that would be less apt to cause HSR, hypersensitivity reactions.

The bottom line, at present, this is 1990, Your Honor, six years after the trials are halted, and Cremophor was thought to be the culprit of the anaphylaxis. The answer was, at present, there is no suitable substitute for

Cremophor.

Indeed, Dr. Sparreboom and others wrote, in 2001, it is of interest that in early studies conducted by the National Cancer Institute, we're talking now about the 80s, paclitaxel was not effective in several tumor models when given intravenously as a solution in polyethylene glycol, or 10 to 15 percent Tween. Now, you'll hear about Tween a lot. That was polysorbate 80. It wasn't effective, suggesting the Cremophor-based vehicle is essential for in vivo antitumour activity.

So as of 1990, and even years beyond, what did the skilled artisan say? Well, we can't find a formulation, alternatively, to Cremophor and it appears that it's essential for in vivo activity.

Now, who is Dr. Sparreboom, Your Honor? I want to pause for a moment because it's important to recognize you will hear in some of the articles by Dr. Sparreboom, we believe you will hear his testimony, it will be played by us. Dr. Sparreboom is not a named expert for Hospira in this case. However, he is an expert formulator. Dr. Sparreboom is the man Hospira hired to do all of the work on the formulation that they've applied to the FDA to make that they say doesn't infringe our patents. He found that Sanofi made major advances in what we did.

Now, what did Sanofi do, Your Honor? Well, the

inventors, Dupechez and Bastart rejected the conventional wisdom. They concluded the best approach was polysorbate 80. But in getting there, they tried many things Your Honor. And you will hear about these. They tried emulsions, micellar solutions, mixed micelles, intralipids and microemulsions and solvents and co-solvents. You will hear more about them. I list them only categorically so you know even though the inventors believed polysorbate worked when no one else did it, it hadn't been tried by Bristol-Myers Squibb and truly eminent scientists at the National Cancer Institute to replace Cremophor.

Still, how you formulate docetaxel now, this is the second molecule, this is a task. It's tough. It's very tough. It's a great challenge.

Now, ultimately, the inventors decided to proceed with formulation of polysorbate 80 and ethanol for two reasons. One, the physical stability testing showed that polysorbate 80 and ethanol could be made into an infusion bag without precipitating too soon. Again, Your Honor, only way to give these taxanes is a perfusion in a bag, in the vein.

Now, but it can't precipitate out, judge. Because if it goes into my vein and five minutes later it forms a clump, it precipitates. Phlebitis, clot into the heart. It doesn't make it to the cancer, I die and my

cancer doesn't get any better. So stability is critical.

The preclinical tests also showed that the docetaxel in test-tubes acted on the tumor. So we knew we could get stability, and we could get it into, it would work on the tumor. So it was chosen as a candidate to go into toxicology studies.

Now, Your Honor, you will hear from our toxicologist and the reason is because every drug formulation in the world always goes through toxicology. Why? We try it on animals first to see if we have a possible candidate for humans. And it's part of any formulation. And also you have to figure out what dose you start at.

And, Your Honor, there is only one term I think you really need, we really need to focus on around it's called the maximum tolerated dose. Basically, we tested this dose on mice and drugs and what they find, toxicologists find out through the doses is what is the maximum dose the dog can tolerate before the dog dies or develops serious problems. And then some fraction of that is the first human dose. But we need to know something else, judge. We need to know what is called the effective dose because the effective dose is the dose you actually put into a human being so it will cure the cancer.

Now, here is the conundrum. If the maximum

tolerated dose is higher than the effective dose, that means I might succeed. Because that means I'll get effectiveness. Here is the cancer before I get to the maximum tolerated dose and kill the human being or cause them harm. But if that maximum tolerated dose is below the effective dose, that means I'm going to hurt the patient or maybe kill them before I can get the cancer.

So that is the conundrum, not what happened when we went into animal testing. Bad news. The dogs died.

And here is what we found out. The highest nonlethal dose in the beagles was 30 micrograms per meter squared. For some reason, when they do these drugs, they don't care about our weight. It's surface area and that is what the meter squared was all about. What we knew we had to get to an effective dose of 60 to 100. So here was the problem Sanofi faced they thought they had an active compound they give it to the animals the dogs died or have serious problems about 30. And by 70 milligrams they were all dying precedent. And yet we knew we had to get between 60 and 100.

Well, there was no expectation of success at that point. The company was discouraged. Some even talked about cancelling the project.

Dr. Rodricks, truly eminent toxicologist and Dr. Parks will tell you that based on the dog tests, the

only expectation any reasonable skilled art Sanofi would have was failure, because you can't get to the effective dose.

You might ask judge why do we pick dogs? Because scientists and the FDA said the dogs, sad as it is, we have to work on dogs as the best indicator of how a drug will go in humans. So when the dogs die, it's not a good sign. And when the dogs died in an amount that is below our effective dose, things don't look good.

Now, what we did was we went back to the drawing board at the same time that the inventors pushed ahead. We went back to the drawing board and we tried other formulations, including the form of the etoposide formulation that these defendants say render our claims obvious. Now, the prior etoposide formulation in the prior art was different than what we tried, but we tried something very similar to that formulation with the excipients and they all failed.

Now, at that point, we proceeded through carefully with the clinical trials and what Sanofi did was go down to five milligrams.

The lowest possible dose virtually you can start with humans.

Now at the same time this happened, Your Honor, there was another interesting discovery that took place at

Sanofi. And that was docetaxel was in very short supply. It's always been a hard molecule to synthesize, and Sanofi needed every bit it could get to perform the tests. So Mr. Bastart was asked to recover the docetaxel from old experiments so we could reuse it each time and it was thought at the time that you needed ethanol to maintain the docetaxel in solution.

So Mr. Bastart goes to the lab, he evaporates off the ethanol because conventional wisdom is ethanol was necessary for solubility. You evaporate off the ethanol, the docetaxel will precipitate out, fall down to the bottom of the glass in the beaker in a lump. He did it. Not precipitant. Nothing happened. Totally against conventional wisdom.

He was concerned. But fortunately for us today, instead of throwing it away or being disappointed at a failed experiment, he had it tested and lo and behold they found docetaxel was still in solution. In other words, the ethanol was not essential. And that allowed us ultimately to develop a formulation that had less ethanol.

Now, what happened when the clinical trials began with docetaxel? Your Honor, against all this bad news of the dogs dying, I'm happy to report that the world actually had good news at this point. That contrary to the expectations that experts, independent experts will tell you

would have been one of failure, we were able to gradually increase the dose from five milligrams to 15 to 20 to 30. And the bottom line, ultimately, we found we could get to the effective dose.

You know what else we found, Your Honor? Anaphylaxis, the dreaded either injurer or something from which you can die, disappeared. In Phase I and phase II trials, you will hear there was either no anaphylaxis and no premedication required or it was very minor, less than .6 percent. But even today, when you give Taxotere now, the dreaded shock cart is gone.

Now, the good news does not stop there, Your Honor. So keep in mind what we find is anaphylaxis is gone and we can reach the effective dose with a molecule that is twice as potent as Taxol. But now we also find that there are unexpected benefits not known in 1991.

First, the polysorbate 80 clears the bloodstream faster. Better pharmacokinetics, linear pharmacokinetics. Dr. Burris will tell you linear means the more I give, it's a direct correlation of side effects so if the side effects are bad, I lower the dose.

Also, works better for drug to drug interactions. Now, why is that so important? Well, Your Honor, breast cancer that afflicts millions of women. Docetaxel, Taxotere is the drug of choice for many. But it

has to be given with a drug called doxorubicin which can interact and can cause heart problems and cause a dangerous reaction. But, unexpectedly, we found that doxorubicin gets along very well with docetaxel. Indeed, Your Honor, neuropathy and other problems that were caused with Taxol, lessened with Taxotere, so we have no anaphylaxis or virtually none.

We have effective dose of Taxotere. And remember, when we started with Taxotere, docetaxel, that molecule was twice as powerful. So we're giving an patient a molecule in a formulation with polysorbate 80. And this is critical, the formulation of it, that allows it to be administered, and we get the unexpected benefits as well.

Now, here is Dr. Sparreboom again; Hospira's consultant. Here is what he wrote in 2003. Overall, our results suggest that the relative systemic exposure to Tween 80, that's polysorbate 80, in humans, is much lower than with Cremophor EL as a result of different rates of elimination. This is consistent with studies reporting that the use of Cremophor as a formulation is more likely to result in drug interactions and excipient related toxic side effects, including hypersensitivity reactions, and neuropathy.

Cremophor did, but not polysorbate 80.

Now, not surprisingly, Your Honor, we submit

they want to copy our product. They will tell you it's not a copy. But let's be clear. The big three ingredients are docetaxel, the molecule, polysorbate 80, and ethanol. And they have more. They add two, citric acid and PEG 300. That is Hospira. Apotex adds only PEG 300.

Now, Dr. Sparreboom tested polyethylene glycol with ethanol and docetaxel. He tested docetaxel, polysorbate 80 with citric acid. So he did it with PEG 300, citric acid and he tested the big three alone. You know what he found? No clinical difference. No effect.

Now, Your Honor, that is a brief history of Taxol that led to Taxotere. And that is why the patents on this formulation are so important.

So we, for all intents and purposes, we got rid of anaphylaxis, we got rid of the shock cart. And we have a powerful drug in a formulation that has sold $7.8 billion. You will hear that because of these unexpected properties, Dr. Burris will tell you, is the primary reason physicians, oncologists who treat cancer every day, prescribe it. So that commercial success of $7.8 billion is due to the great activity, no anaphylaxis, and it's also due to these unexpected results. It's a better drug formulation.

Now, Your Honor, I want to turn to infringement. All right. First we'll deal with the '561, Claim 5.

Claim 5, Your Honor, has five elements: a

perfusion that contains approximately 1 mg per millimeter of docetaxel, less than 35 milliliters of ethanol, and it's capable of being injected without causing anaphylaxis or alcohol intoxication manifestations.

Now, Your Honor, you will hear about a perfusion. And in accordance with Your Honor's ruling, we will produce extrinsic evidence. But this is what you will hear in accordance with, and very similar to, this agreed upon construction, which I understand the defendants say isn't agreed on anymore. And you are going to have to decide.

Here is what the doctors will tell you. An perfusion, particularly in the context of this patent, the '561, is a solution suitable for infusion into patients including at least active pharmaceutical ingredient -- that's the docetaxel, that's the molecule -- and an aqueous infusion fluid such as physiological saline or glucose.

Now, Your Honor, you are going to see references in the patent also to perfusion and perfusion bag. When you hear this testimony -- and I'm not quite sure what the defendants are going to say about a perfusion. But remember this. On this, the experts cannot disagree. The only -- we're talking about the '561 and the '512 patents. It's a taxane, docetaxel formulation of polysorbate 80 to treat cancer. There no question that is what the patent is about.

There is only one way to get it into the human body: a perfusion in an IV bag, into the veins. That's the only way. So we submit you can't read it any other way.

And when you see the definition, which I think the Court will accept, suitable for infusion into patients, you will hear there are three criteria that all true drug formulators understand, true drug formulators understand. If you want to talk about suitability for infusion into patients, you have to have three things with a cancer drugs:

Physical stability. This molecule that will hurt you if it's not in solution. It's got to stay in solution, it's got to be stable.

And it's got to be reasonably safe. After all, we're trying to cure the cancer, not kill the patient.

And it's got to be effective, meaning it's got to get to the site of the cancer.

All right. And you might notice, on the docetaxel box from Hospira, we've highlighted it. They even tell the world, for infusion only. For IV infusion only. It's the only way. Can't give it by mouth, or any other way. So there will be no doubt we submit that they have a perfusion.

Similar, Apotex label says for intravenous infusion only after final dilution. It's a perfusion, in the bag.

Now, Claims 2, 3 and 4 are, we think, very straightforward. Your Honor, what we have on the right-hand side is calculations of Hospira's perfusion at maximum concentration.

You see that the amount of docetaxel is .74 milligrams per milliliter. That is less than one. And they have ethanol of 17 milliliters per liter. That's less than 35. And polysorbate of 80 of 17.8 milliliter. That is less than 35.

I don't think there will be any issue of that. If necessary, Dr. Burris can show you how to do the math, but I think on Claims 2, 3 and 4, the defendants will admit they have it. They have to. The simple math demonstrates it.

Similarly, the Apotex product in each case the amount of docetaxel, ethanol and polysorbate 80 is less than the amounts called for in the claims.

All right. Let's turn to Element 5, Claim 5. Reasonable expectation of being injected without causing anaphylaxis shock or alcohol intoxication.

Defendants, their own labels that they want the FDA to approve say that anaphylaxis is very rare. Okay? They have the same side effect profile as Taxotere, which is well under one percent of the patients administered Taxotere suffered anaphylaxis.

Dr. Sparreboom, their consultant, again, was asked for deposition.

"Question: Are you aware of any anaphylactic manifestations that are associated with the Mayne Pharma docetaxel formulation?"

That's the formulation, judge, they applied to the FDA for that they want you to rule in their favor on.

"Answer: No."

And Apotex's experts agree that both Taxotere and Apotex perfusion can be administered without fear of anaphylaxis.

Now, Your Honor, you will hear a lot from the defendants of anaphylactic manifestations being some kind of symptomology.

But what I think you will decide is that anaphylactic manifestations is anaphylaxis. That's what doctors and nurses on the front line will tell you. Your Honor will see when you compare it with the patent that when we claimed the invention over Cremophor, we talk about getting rid of the anaphylactic reactions. Well, the anaphylactic shock that Taxol had, Your Honor, was deadly and serious injury.

With respect to alcohol intoxication, I think this will be pretty important, all the experts in the case have agreed that Hospira's and Apotex's proposed

formulations can be administered without causing alcohol intoxication manifestations.

As Your Honor knows, there is a huge debate among the parties on "free or essentially free of ethanol." Suffice it to say that the amount of ethanol in both Hospira's and Apotex's formulations is well below the APA threshold for intoxication. I really don't think this will be fought over in terms of infringement.

Your Honor, let's talk about Claim 2 of the '561 patent and Claim 10. You will see, Your Honor, the language "consisting essentially of." That's the battleground. Your Honor has construed consisting essentially of as, it means the listed ingredients and may include others that don't affect the basic and novel properties.

As I covered earlier, what do we have here? You can see the Hospira perfusion and the Apotex perfusion prepared for and disclosed formulations for Taxol. They all had docetaxel, ethanol, and polysorbate 80. As I said earlier, Hospira has PEG 300, citric acid, Apotex has PEG 300.

Our position is PEG 300 does not affect the basic and novel properties.

Your Honor, it is a bit of a quandary here. It will be interesting to see how the testimony actually plays out. Hospira's experts are going tell you that PEG 300

increases the physical stability of the perfusion. That will be their position. Apotex's experts are going to say it decreases. I am not sure about that. You would think they could have gotten together on that one.

In any event, both Hospira's and Apotex's label identifies the same stability as Taxol. And the testing done by Sparreboom shows similar stability to that reported in the patent.

In other words, Your Honor, when you look at the proposed label that Hospira and Apotex want the FDA to approve, they do not assign any significance at all to the label that they are going to give to physicians to the presence of PEG 300.

In fact is, Sparebroom has conducted studies, and you will hear in his testimony, where he has concluded that the addition of PEG 300 has no clinically relevant effect.

Let's turn to citric acid. That doesn't affect the basic and novel properties. Here the Hospira experts claim that it improves the chemical stability in the stock solution. Apotex's expert says it doesn't. Of course, Apotex doesn't have citric acid. I don't know if they are helping Hospira or not. But they are telling you it doesn't materially affect the formulation. In all cases it is suitable for I.V. perfusion, and Mr. Sparbroome says, no

clinically relevant effect.

Your Honor, if we can, let's turn to the '512 patent. We assert Claims 7 and 33.

Claim 7, there are three elements, a docetaxel dissolved in polysorbate essentially free from ethanol. There is no question that both of these products have docetaxel dissolved in polysorbate. The debate will be whether or not the perfusions, Apotex and Hospira, are essentially free of ethanol.

Your Honor construed "essentially free or free of ethanol," which is right from your claim construction order, that for a stock solution it is no more than 5 percent ethanol by volume, and for a perfusion, it is the same amount of ethanol as a stock solution with no more than 5 percent by volume.

Your Honor will remember at the pretrial conference and the motions in limine, this was a subject of intense debate.

Our position is it is fairly straightforward. In accordance with your claim construction, the fact of the matter is you are going to see the versions, the perfusions that Apotex and Hospira have have less than the amount of alcohol, 2.5, than you would have if you started with a stock solution of 5 percent.

We thought this would be the best way to help

explain this.

The parties agree on No. 1 and No. 2, Your Honor. If you start with a stock solution of 2 milligrams per ml of docetaxel and 5 percent by volume, which you said is a stock solution, it can't be more than that, that that is essentially free. You have experts Myrdal, Williams and Kibbe. These are all defendants' experts. A perfusion with one milligram, half of that, therefore, with 2.5 percent by volume ethanol is essentially free. So, take half of one, 50 percent, get one from 2, half of that. Now we have something the parties agree on.

Lets look at the bag. Here is what we know. We know that the maximum concentration of the docetaxel in both Hospira and Apotex is .74 milligrams per milliliter, not 1. So you have to do a little math. When you reduce by a fraction, you go from 1 milligram to .74, you take 2.5 down by the same amount, it's 1.85.

By that simple calculation, Your Honor, we contend that it becomes clear that with .74 milligrams per ml of docetaxel, if you have 1.85 percent by volume or less of ethanol, you are essentially free.

We have calculated the 250 milliliter I.V. bag because that's the size bag that Hospira and Apotex tell the physicians to administer, and in many hospitals today that is the size of the bag that you get on the stand to give

them.

If that is true, that is 185 milligrams of docetaxel in that bag and you have 4.62 milliliters of ethanol.

Let's see what happens in the bag.

As you start with Hospira's solution through a series of dilutions they do, they get 4.25 ethanol, 1.7 percent. In other words, less than 4.62.

And therefore, in a 250-milliliter bag, they have 180 milligrams of docetaxel, 4.25 milliliters of ethanol. But 4.25 is less than 4.62. It is essentially free.

Apotex's perfusion ends up, after going through its various dilutions, to have only 1.12 milliliters of ethanol. Again, that is less than 4.62.

Your Honor, the elements of Claim 33, again, we believe, are very clearly infringed. The elements are a stock solution comprising docetaxel 10 to 200 milligrams per milliliter dissolved in polysorbate 80.

As Your Honor has said, stock solution is construed to mean a concentrated solution. And here is what they have, Your Honor. Hospira has 10 milligrams per ml. That is between 10 and 200. And it's dissolved in paclitaxel.

Similarly, the Apotex premix has 10 milligrams

per ml of docetaxel. That is between 10 and 200. It's dissolved in paclitaxel. That's what they do every time. That's what their instructions for use do. That's what they have told the FDA. That's what they tell doctors and hospitals.

There is no doubt about how these are used, Judge. Contributory inducement to infringe is very clear. There is only one way to do this to get this into the patient and there is only one thing you can do with these products.

Your Honor, I want to turn to validity quickly.

Your Honor, as you know, they will go first on their invalidity challenge. Your Honor, all I can tell you is, as you can see from the slide, we are presented with nearly 1,000 pages of reports from the defendants in toto. Six references and 18 combinations is what we had to deal with during the discovery. We don't know for sure, because it continues to be a moving target, exactly which one of these they are going to pick and which of the combinations. So I ask Your Honor to be patient with us.

Our answer to these will have to await our portion of the case, because, as Your Honor has ruled, the initial invalidity presentation on at least these references is Hospira and Apotex's.

Our opening case will be infringement and the

objective indicia of nonobviousness, since, of course, we have the burden of production on that.

But their art falls into three categories, Your Honor. Remember, we are dealing with a clinical formulation, not test tubes here. Clinical formulation. The '561 and the '512 patents claimed a formulation for infusion into a human being.

I just want to highlight something, Your Honor.

There is the drug discovery portion in light (indicating), where they first have to put the molecule into a Petri dish or a test tube to see if it has activity.

But then there is the drug development phase, where you have to consider the toxicology and stability and the safety of the drug before you put it into human beings.

We are not test tubes. We are not Petri dishes. And I can tell you this, and you will hear it from our experts, there have been hundreds in the world and thousands of molecules that have gone into Petri dishes, shown activity, and crashed and burned on the floors of laboratories as they tried to get it in patients.

So when they start talking to you about prior art that supposedly renders our invention obvious and it's stuff out of Petri dishes, I ask the Court to remember this case is about real people and human beings and clinical formulations.

They have only one that they have offered. They also have failed efforts to develop clinical formulations and wholly unrelated clinical formulations.

Let's deal with the briefing.

They say the old etoposide made in the early eighties anticipates or renders obvious our claims. Remember, Your Honor, as I cover the history, this is the etoposide that existed when the clinical trials were halted and BMS, Bristol-Myers Squibb, and the National Cancer Institute knew about the etoposide formulation because Bristol-Myers Squibb had it and it had polysorbate 80 in it. But they didn't go to polysorbate 80. Why? It wouldn't work.

Of course, etoposide is not a taxane, Your Honor. And what you are going to hear in this trial is taxanes are a tough new group. The good news is they are powerful molecules, in the right formulation, for the treatment of cancer. The bad news is they are very tough to formulate. So saying they used polysorbate 80 with an etoposide, that doesn't tell you anything about whether or not it will work with a taxane.

As I pointed out, Your Honor, I think this is so significant, and that's why I highlight the facts. You are going to have to decide, as you always do, being the Judge in this case and the finder of fact, between conflicting

experts and conflicting facts. But we respectfully suggest you look at the facts and draw the reasonable inferences therefrom when life really took place. And ask yourself, if you were Bristol-Myers Squibb and the National Cancer Institute and you thought you had a great new molecule in paclitaxel, Taxol, and within months of the clinical trials starting they were halted due to death and anaphylaxis in patients, and the word was, Cremophor is the culprit, if it was so obvious, you would have just said pick polysorbate off the shelf, stick it in, man, we are off to the races and we are off fast.

They didn't do that, and we know they knew because they had it.

Finally, Your Honor, when we had trouble in our own clinical trials with the dogs dying and not looking like we could get a sufficient dose to treat human beings, we tried the etoposide formulation with docetaxel and Mr. Fabre, one of the inventors, will tell you, it failed. It failed.

Now, then they have failed clinical formulations they will offer as prior art. Tarr and Yalkowsky worked hard in the late eighties. They tried pluronic L64. They tried triacetin. They tried forms of emulsions. What were they doing, Judge?

They were trying to find a substitute for

Cremophor which was thought to cause anaphylaxis. They all failed. Not enough stability for administration intravenously and both too toxic.

Your Honor, you will hear from our experts that Tarr and Yalkowsky are among the leaders in their field, working in the late eighties. They couldn't do it.

So just remember, when Mr. Hurst and Mr. Dresner tell you how obvious our invention is in light of this prior art which was on their list, just remember, they failed: no physical stability, too toxic.

Then they go finally to the third category. This is work unrelated to clinical formulation. They are going to show the Gueritte-Voegelein article and they are going to say, Hmm, that was in vitro work, but polysorbate 80 and ethanol, there is a sentence in there that talks about it. They are going to say, aha, there it is, Judge. Polysorbate 80 and ethanol, invention was disclosed, any skilled artisan would have remained.

Let meet you something about GV.

It's in vitro -- we are in the tubes -- and extremely low concentrations of docetaxel. It wasn't a perfusion and it wasn't suitable for clinical use.

Your Honor, this is what I am going to say about Gueritte-Voegelein. You will hear a lot about this, too. This case is not about putting low concentrations of

docetaxel into test tubes and Petri dishes.

It's about stable perfusions for administration to patients. And just remember, many, many Petri dish examples have crashed and burned.

Now, Your Honor, I want to turn to, very quickly, to indefiniteness and lack of enablement. Your Honor, I am almost done. I am moving as quickly as I can. But, you know, these two defendants have thrown a lot at me, and I have got to take it on.

On indefiniteness, Your Honor, the defendants say anaphylactic manifestation is indefinite. Judge, you are going to hear from Dr. Burris, Dr. Howard Burris, who was there when Taxol went into Phase I clinical trials. He was there when they were halted. He was a principal investigator for Taxotere, the drug we are here about, in San Antonio, Texas.

He has lived with both of these drugs and prescribed them more than any of the defendants' experts. He was the doctor who administered the first dosage of Taxotere in the United States, the second in the world. The first one was done in France, the second one here by Howard Burris, our first witness here.

He will tell you, anaphylaxis, a doctor knows it, they are trained to know it, they know it when they see it, and you better act fast or the patient will die. He has

witnessed two patients on his watch die from anaphylaxis.

So some of these formulators and some of these academics attempt to tell you that anaphylaxis is indefinite. Listen to the people who are on the front line every day and fight the fight and walk the walk and don't just try to talk the talk.

You will also hear from Nurse Handy, oncological nurse. We call her for a specific reason, Your Honor: because the nurses are really on the front line. They are the ones that have to monitor these. She says there is nothing indefinite about anaphylaxis, if you are in the real world and if you really treat cancer patients. There is nothing indefinite about it.

And thank goodness for us that doctors and nurses aren't indefinite or uncertain.

Lack of enablement? Well, not much to this. There is a suggestion, though, that Claims 2, 5 and 10, that you wouldn't know how to practice the claim and avoid anaphylaxis. And Claim 33 is not enabled because you can't make up a stock solution of 200 milligrams per ml. We will deal with that and show that you can.

Your Honor, on inequitable conduct, that's been a moving target for us. As you know, even several weeks before the pretrial conference, amendments were being filed. I will just say this: Defendants' burden is high. We will

respond to whatever they put up. I ask the Court to remember the Federal Circuit has warned us that it is a plague on the Patent Bar. We are not clear what theories are being advanced. Rest assured, whatever they are, we will be prepared to respond.

Your Honor, let me conclude by telling you this, reminding you of this.

These are the expected results by our invention we hope to get. We avoid anaphylaxis without premedication. We do give some premedication, Your Honor, with Taxotere, but do not be fooled. What we found with Taxotere is that sometimes you get edema, excess fluid, because you take it a lot because it's actually a successful drug. For that you take some oral steroids before you start. But that's not the premedication that Taxol had. That is not the glucocorticosteroids and antihistamines to keep you from going into anaphylactic shock and dying.

So I ask that you not be fooled if Mr. Hurst or Mr. Dresner say, well, Your Honor, Taxotere has premedication. One has nothing to do with the other. One is an annoyance, a complication, it's fluid gain, because Taxotere can be administered a lot. The other, that is still given today with Taxol patients, is the premedication you have to get in your vein for an hour.

These unexpected benefits of polysorbate 80

clear the blood stream faster, better pharmacokinetics, and reduces clinical side effects, drug-to-drug interactions, and neuropathy.

Your Honor, Dr. Burris will tell you that physicians prescribe Taxotere due to the expected and unexpected benefits. That's why they do it. And we believe you will put a lot of stock in the commercial success. In addition, this drug has received praise from the world.

In closing, because of the hard work of three men, we have today a formulation known as Taxotere which overcame serious problems in the prior art and saves lives today.

Thank you, Your Honor.

THE COURT: Thank you, Mr. Pappas.

Mr. Hurst, are you going first?

MR. HURST: Yes, Your Honor.

If I may hand up the opening statement, Your Honor?

THE COURT: Please do, Mr. Hurst.

You may proceed.

MR. HURST: Jim Hurst on behalf of Hospira, Your Honor. I am going to organize my comments this morning based on this table of contents. I am just going to kind of walk through it go.

Before I start, I think, after listening to Mr.

Pappas's remarks, it is probably worth reminding the Court of what the case is actually about. It's not about the cancer drug docetaxel itself, the cancer compound. That's the subject of a different patent. It's not challenged in this proceeding.

This case is not about developing, for instance, an effective dose of docetaxel to treat cancer patients. That's the subject of a different patent, too, that's not at issue in this proceeding. This is not about methods of treating cancer with that chemical compound. That is the subject of different patents. And they are all worthy inventions and they were very valuable inventions. It doesn't happen to be what is at issue in this case.

What is at issue in this case is literally the pharmaceutical formulation in which the drug resides. And that's all this case is about, the pharmaceutical formulations. And I want to talk initially about Hospira's product and it's pharmaceutical formulation.

This is not your traditional case between a generic drug company and a brand drug company, Your Honor. I know you handle a lot of these cases. We did not file an ANDA application. We filed a New Drug Application called a (b)(2). It's when you have the same active ingredient but you change the formulation, which is what this case is about. It's when you change the formulation so much that

the FDA considers it a new and different product and requires you to file essentially a New Drug Application.

So here are the products. Just a little background on the accused products.

You are going to hear from our formulator, her name is Julie Liu. Her task was to make a formulation better than Sanofi's formulation. And she achieved that goal, Your Honor.

Here are just three differences between the product that she achieved by changing the pharmaceutical formulation, which is what the case is about.

She has added ingredients that made things better. Number one is at the top here, this is Sanofi's product. It is a two-step product which requires mixing and infusion. Let me tell you what I mean by that. They sell their product in two bottles. They couldn't get it all together in one bottle and make it work. So one of those bottles has the active ingredient of polysorbate 80. The other has an ethanol and water.

Here is what the medical practitioner has to do. Step one, they pull the liquid out of one of the bottles, put it in the other bottle. Then they have to mix it by going like this (indicating) for 45 seconds, back and forth, back and forth.

Because these water and soap -- surfactant is

just soap, that's what it is -- it creates foam, which causes dosing problems. For instance, say you go back and forth like this (indicating) and you end up with --

THE COURT: Back and forth like this is shaking the bottles.

MR. HURST: Actually, they say don't shake it. You just go up and down, up and down. That's what they tell you to do for 45 seconds. But it produces foam, because say you end up with 3 milliliters of foam, 7 milliliters of solution, but you have to give the patient 8 milliliters.

You either misdose the patients or you wait until the foam goes away. So it's a big deal.

And after they make that mixture, they call that a premix. That is what Sanofi is calling their stock solution in this case, the two bottles put together. After that, it gets injected into the infusion bag, and that's the second step. So there are two steps. Our product, one step. It's altogether in one bottle, ready to use. It goes directly into the IV bag.

Second advantage. This stock solution, after you put them both together, Sanofi's product, it lasts for eight hours. That is according to the label. Our stock solution, two years. It's a big difference.

Another difference? Single use versus multiuse. Let me tell you what I mean by that. You don't give the

same dose to every patient. They're prescribed by the size of the patient. You would have a larger dose than a smaller person.

One person might need three and-a-half bottles of the premix. One person might need one and-a-half bottles. There is often leftover drug. A half a bottle, three quarters of a bottle, a quarter of a bottle, what do you do with it? With Sanofi's product, you throw it away. This is a big deal because it's an expensive cancer drug because you cannot reuse half empty bottles. Our product is multiuse, so if you end up with a half bottle left over after you treat one patient, you don't throw it away. So it's not only a generic drug that will make the price cheaper, it also avoids waste.

So it's an improved product. There is no doubt about it, and I don't think there will be any dispute in this courtroom about that subject. It's an improved pharmaceutical formulation, which is what the case is about.

Now, let me talk about the claimed invention briefly, Your Honor.

Mr. Pappas spoke a lot about the importance of docetaxel itself, but that is not the invention. The invention according to the inventor was as follows: The present invention then makes it possible to replace the Cremophor by a polysorbate. Okay? Those are both

surfactants so they swap one surfactant for another.

Now, every patent has to have what you call, I like to call it a "gee whiz." What is your departure from the prior art? What is the novelty? What is the innovation? What is the invention? This is what they call the true invention, swapping out Cremophor for polysorbate.

Now, two points on that swap out, Your Honor. Number one -- and this is important -- there was only two choices. There was only two choices for surfactant. No expert in this case has identified any FDA approved injectable drug using surfactant as a drug other than polysorbate 80 and Cremophor so there was only two choices.

When you make a pharmaceutical formulation, judge, you don't pick ingredients that have never been tested in human beings. You pick ingredients that have been approved and tested in human beings, and both of these surfactants were available but none others, so there are only two choices.

Now, between those two choices, Your Honor, the use of polysorbate 80 with docetaxel was already disclosed in the prior art before they filed their patent application.

This is we call it the GV reference, just to avoid the pronunciation issues, frankly, but it's in March of 1991. It's in the prior art. There is a story here, Your Honor. Sanofi went into clinical trials with this

drug. They had a patent on the drug and they announced to the world that they had a better cancer drug than the prior art, paclitaxel. They said of all the compounds we examined, this Taxotere product was selected for evaluation as a possible anticancer agent.

Now, here is the piece that Mr. Pappas was dismissing. In this article, they say, moreover, Taxotere showed a better solubility in an excipient system, polysorbate 80 and ethanol. So they are disclosing the swap-out already in their article, announcing to the world their new cancer drug. They said polysorbate 80, they didn't say Cremophor.

Now, one thing that Mr. Pappas said. He said this was in vitro testing. Remember he said in vitro testing? That was that article. That is not a solution for in vitro testing. In vitro testing is when you test the drug in cancer cells. You don't use polysorbate 80 and ethanol when you test the drug in cells because it would kill the cells.

They were disclosing their pharmaceutical formulation. They disclosed it in the prior art. Polysorbate 80, not Cremophor. It's disclosed.

Now, let's just talk a little bit about surfactants, because there is going to be a lot of discussion in this case about surfactants.

It's Formulation 101. Surfactants are literally tied to college level pharmaceutical formulation. It's as simple as this. You have a solid particle that will not dissolve of in water. Stir it around, it's still there. You add a surfactant.

And what happens? That solid particle that otherwise wouldn't dissolve in water suddenly dissolves in water. It's really that straightforward.

Now, properly motivated, a lawyer can make even something that simple seem very complicated. I know you have seen it, Your Honor, and you are smiling. But let me give you an example. Let me explain the process for you.

I want to explain a process that is designed to remove hydrophobic lipid residue from a planar inorganic crystalline oxide surface by the use of an amphiphilic -- I can't even pronounce it -- surfactant in an aqueous solution to form micelles and thus successfully dislodge the hydrophobic residue.

Now, what I just described to you sounds very complicated. I described washing a dish. Anything can be made to sound complicated.

You know, you use dish soap at home. It's a surfactant. That is what it is. You put your oily plate in the water before the surfactant, you pull it out. The oil doesn't go away? Why? Oil doesn't dissolve in water. You

throw a little soap in there, you get a clean plate. That is what surfactants do.

Now, do you need to know the underlying science to even understand you can wash dishes that way? No, you don't.

Let me give you an example of what is going to happen in this case. The plaintiffs are going to bring to you a gentleman named Dr. Kaler, okay? He is not a pharmaceutical formulator. He doesn't claim to be a pharmaceutical formulator. He is an expert in surfactants. He can talk about surfactants at the molecular level. He can talk for hours about chemical structural interactions between surfactants and compounds and it's all very complicated.

What we're going to bring to you is a pharmaceutical formulator. For instance, you are going to hear from Dr. Myrdal. Dr. Paul Myrdal. He is from the University of Arizona, and he is going to explain that surfactants are very simple and basic for pharmaceutical formulators. And based on what was taught in the prior art, it was an exceedingly straightforward choice to use polysorbate 80 rather than Cremophor for this drug based on what was taught in the prior art. And that is the whole invention, swapping one for another.

So let's talk about the prior art. I have a

time line, too. And I'm just going to walk through it as I go.

Now, the paclitaxel formulation, it was set in 1980, Your Honor. That is when it was set. And there was only two surfactant choices then as well and they chose Cremophor to go forward with rather than polysorbate. There was two choices, they picked one.

Now, how does it work for taxanes? Really, it's a very actually simple pharmaceutical formulation. There where only two ingredients. It's called a co-solvent system, and it works for taxanes. It works for this ingredient and others, ethanol plus a surfactant. Why? A taxane doesn't dissolve in water but it dissolves readily in ethanol, and that was well known. So you needed to put it into a liquid, so you put it into ethanol.

But guess what else? Taxol also dissolves in surfactants. So it will actually, the surfactant acts like a solvent. It will help dissolve the drug. So in the stock solution, it's a co-solvent system. There are two solvents, ethanol and a surfactant, which in 1980 they used Cremophor.

But the surfactant also plays an important role later in the perfusion. So you take this bottle and inject it into an IV bag, which is water based, and then the surfactant, when exposed to water, helps to keep the drug in solution. So it plays two roles. It's a solvent in the

stock solution and it acts as a surfactant in the perfusion.

Now, as Mr. Pappas mentioned, they ran into -- they started clinical trials with paclitaxel in 1983. I think our time lines disagree. I'm taking mine from Rowinsky. That is an article that sets for the entire time line.

But they went into Phase I clinical trials, and they did it without premedication, but they started to see, Your Honor, allergic reactions. Okay? It's like when some people react violently to a bee sting? Very similar. These allergic reactions were occurring in these early clinical trials: Hypersensitivity reactions, anaphylaxis symptoms, okay? And they didn't know initially what it was.

Even by the mid-1980s, Your Honor -- this is an article from 1986 -- they thought the most likely candidate was Cremophor, but they also thought there was a possibility that the chemical compound itself, docetaxel -- I'm sorry -- Taxol might be causing the anaphylactic reactions.

Now, a very key point for the other side is this. Well, as soon as they saw the hypersensitivity reactions, why didn't they swap then Cremophor for polysorbate 80? That is really one of their main arguments. If it was obvious, why didn't they switch out, swap it out right then and there?

A few reasons, Your Honor. First is they didn't

know it was Cremophor, itself. They still thought it might be Taxol. So why go from the effort from starting from scratch because that is what they thought they would have to do. Start from scratch with a new formulation, restart all the clinical trials with a new formulation even though they weren't sure it was Cremophor itself or not.

Another reason is when they started seeing the anaphylactic reactions in 1983, they didn't know whether swapping it out for polysorbate 80 would actually fix the problem, because the art hasn't started to conclude that polysorbate 80 would actually reduce hypersensitivity reactions. That comes later in time. So why spend all the time reformulating and swapping out if, at the end, you might not solve the problem anyway?

And you know what the fix was? The easy fix, the cheap fix, and the fix they went forward with, was premedication. They gave the patient steroids instead of reformulating. And starting from scratch and maybe not solving the problem, all they did was give the patients premedications, steroids. And that made the symptoms more manageable, okay?

So when you give somebody steroids before they get Taxol, it reduces the hypersensitivity reactions. This product is still on the market today. It's still a decently selling -- it sells pretty well still. It still has

Cremophor. They still give premedications. So that solution not only is what they did, it worked, and still works today, okay?

So moving forward in time. Now, we go from the prior art compound to the new compound, docetaxel, okay? And this is a critical point, Your Honor, given the opening statement from counsel. Sanofi filed a patent application on docetaxel and docetaxel formulations. This is their patent on the drug, itself.

We're not challenging this patent. It's not one of the patents at issue here. So when Mr. Pappas is talking about all the great things that this drug does to treat cancer? That is a different patent. That is this patent. We're not challenging this patent. They had their entire patent monopoly on this. They got what they're entitled to under the law. It expires on May 14th, 2010. And we have no interest in going into the marketplace until after it expires. It's actually a good patent. It's a real invention.

But, importantly, Your Honor, not only did they claim in this patent docetaxel itself, they claimed pharmaceutical formulations really broadly, so the two formulations you have been hearing about, ethanol plus Cremophor, or ethanol plus polysorbate 80, it's claimed in the earlier patent precedent. It's covered by the earlier

patent. Both of them are because they claimed them broadly. They were telling the world we work. They were saying essentially, hey, use any normal pharmaceutical formulation. It's going to work with our drug. That's very contrary to the position they're taking here today in court, Your Honor.

Now, I mentioned before, so what starts happening in the prior art? We're moving forward in time after the Taxol trials, continued with premedication. The prior art starts to report that you know what? You can reduce hypersensitivity reactions by swapping out Cremophor for polysorbate 80. And it's right in the art.

Neither of these references was before the Patent Office. Neither of them were before the Patent Office. The earliest we could find to start saying this outright was the O'Dwyer article in 1984. And what he talked about was the greater frequency of allergic reactions when you compared two compounds, teniposide and etoposide.

What he is saying in this article is you are going to get less hypersensitivity reactions if you swap out Cremophor for polysorbate 80. This is pretty important, too. These two drugs, the earlier drug used -- let me just give you a little context here. Both of these drugs are anticancer drugs. Both of these drugs are administered by IV infusion. Both of these drugs are insoluble in water, okay? Very similar situation. The earlier drug used

Cremophor. The later drug, they swapped out and used polysorbate 80 instead, to reduce, and it did reduce, according to their reports, hypersensitivity reactions. It's the allergic reaction we've been talking about.

That is 84. Now move forward to 1988. This is a doctor from the University of Arizona, Dr. Dorr. He faced the same problem and he used the same solution as Sanofi. He had an insoluble cancer drug called acryniocin and the earlier formulation that they used with animal studies had Emulphor. That is Cremophor, different brand name, same product. That's the same drug.

He said you know what? The reports are that that product, that ingredient might be causing hypertension sensitivities, so let's swap it out. And what did he do? He said look at what this company Sandoz did. I'm going to do the same thing they did. I'm going to swap out Cremophor with polysorbate 80 because that might reduce my hypersensitivity, my allergic reactions.

So just to review the bidding here. This is the Sandoz, swapped out, teniposide to etoposide. Later derivative of the same drug, they swapped it out.

This is the Dorr situation. He swapped it out. He swapped out a Cremophor for polysorbate 80, and he explained why he did it, because he said they had fewer hypersensitivity reactions.

And there is a third swap out in the prior art, and that is the GV article.

Again, the Patent Office did not have this reference, Your Honor. This is the one I talked about. This is where Sanofi's predecessor disclosed to the world their pharmaceutical formulation in the prior art. And this is, in fact, the formulation that they took into clinical trials in June of 1990 and they disclosed the formulation in March of 1991. So it was in the prior art. The swap out was disclosed, which makes three swap outs in the prior art. All cancer drugs, all insoluble, all administered by IV.

And then, only after all that was disclosed in the prior art, Sanofi goes to the Patent Office and says my invention is swapping out Cremophor for polysorbate 80. I'm going to use polysorbate 80 instead of Cremophor. Only after all that was reported in the prior art.

But what else would you do? Okay? There was only two choices, only two choices for surfactant, and clearly the prior art was starting to blame Cremophor for all these sensitivity reactions and the art in the later 80s started to report that polysorbate 80 could improve those hypersensitivity reactions. So what else would you do? You'd swap out Cremophor for polysorbate 80. It's really that simple and straightforward.

Now, I want to address just a couple of

arguments that the plaintiffs have made. They say that people believed that Cremophor was important to the activity, the cancer fighting activity of these taxanes. That was the argument they made. And they put up an article from 2001, Your Honor, to support that argument.

Just to make sure it's clear. They're saying the reason you wouldn't swap it out, you wouldn't swap out Cremophor for polysorbate 80, is they are saying people believe Cremophor was important to making taxanes work. That was their argument.

You're not going to see one piece of paper. There is not going to be one single reference, no lab notebook, nothing from Sanofi that suggests that anybody actually believed that in the prior art.

There is a 2001 article that literally says there was a belief that Cremophor was essential to Taxol's activity, but they cite -- that 2001 article cites a 1992 article, which, by the way, is still not the prior art, it's post-application, and they just miscite it.

The 1992 article says that they do tests. They test Cremophor with ethanol, and they test polysorbate with ethanol, and they conclude that Taxol achieves similar maximum effects using either vehicle.

The later article, '01, which it shouldn't matter anyway because it's not even the prior art, just

miscited or misread the Rose article. The Rose article says the exact opposite: either vehicle works fine for Taxol. So there is nothing in the prior art suggesting that anybody believed Cremophor was somehow essential to taxanes work.

Another thing that Mr. Pappas argued is that people tried and failed. People tried to develop alternatives to Cremophor and failed. And the citation that he gave for that was this Yalkowsky article.

Actually, Yalkowsky was a success. He published his article because he was a success. He wasn't as much of a success as he had hoped to be, which is what Sanofi was relying on to say it was a failure, but his formulation for a taxane, not using Cremophor, by the way, showing people did not believe it was essential to the activity of the drug.

His formulation was polysorbate 80, ethanol, okay? Just like the plaintiffs. And he used an additional surfactant called pluronic in his testing. It worked just fine as a stock solution. And his perfusion lasted for two hours, which is plenty of time for docetaxel which is administered within one hour. So Yalkowsky, he wasn't as much of a success as he had hoped but he was clearly a success, which is why he published his article.

So let's review our defenses.

First, I just reviewed the prior art so I'll be

brief about anticipation, obviousness and inequitable conduct, but look. Here is the alleged invention.

With only two FDA-approved choices, Sanofi chose polysorbate 80 instead of Cremophor. That is what they say in their patent. That's my invention. I swapped it out.

First of all, we have anticipation. That choice was already disclosed in the prior art. They already disclosed the formulation. That is the GV article. That is straight anticipation. It reads on at least one claim, maybe more.

Obviousness. You know, the world has changed since KSR, but just for context, one statement from KSR that I think is particularly apt in this case. A Court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

Polysorbate 80 in the claimed invention is being used for its established function. It's being used as a surfactant. So it's being used exactly as it's intended to be used.

And what was the result? Well, Sanofi went to the Patent Office and said that we achieved something that was exactly what the prior art identified would be achieved. Here is what they said. We did this swap out. We swapped Cremophor for polysorbate 80, and it became apparent that the anaphylaxis reactions were greatly reduced.

That is what they claimed was their kind of "gee whiz." It worked. They reduced anaphylaxis reactions. Well, that is what O'Dwyer said in 1984, that is what Dorr said in 1988. That is what is apparent from reading the Handbook of Pharmaceutical Excipients. And it's apparent from Vidal. That's the French equivalent of the PDR, Your Honor. The prior art said all that already.

And here is a key point. Sanofi knew it all. Sandoz knew it all. Sanofi knew it all. But this is a memo we found in their internal documentation during discovery. This is from December of 1988. Two inventors received this memo.

It starts off, Cremophor is accepted less and less by clinicians and registration authorities and the like.

That was the problem they identified to the PTO. They told the PTO about the first sentence. They cited art saying it was a problem, but they didn't tell the PTO about what they relied on for their solution.

The main piece of art that they relied on for their solution was the Sandoz swap. They say this is why Sandoz, having developed the cancer drug, teniposide with Cremophor, then developed an analogue product called etoposide, in Tween. Tween is polysorbate 80. So they knew about the Sandoz product. They read about it in Vidal. It

was the impetus for the swap because it was successful for Sandoz, and they didn't tell the Patent Office about it.

Now, Sanofi lawyers is saying this art is not material. That is what their argument is. And, you know, it's really, when the main piece of art that you rely for your invention is not disclosed in the Patent Office, that is a problem. It's for the Patent Office to decide whether or not you are entitled to invent an invention over the prior art.

Holding it back and having lawyers argue later it's not material is not how the system is supposed to work, Your Honor, just is not how our system is supposed to work, and, in fact, is highly material and, in our view, is invalidating. And that is why I explained the prior art the way that I did. It was the leader. This swap is what led Dorr to do the same thing and I think what led Sanders to do the same thing.

But the Patent Office never knew about it. In fact, none of the references I have been talking about and relying on, the Patent Office didn't know about any of them. None of that was before the Patent Office.

Other invalidity defenses, Your Honor.

I am going to be brief. There are a lot of problems with these claims. And we set forth the problems, the five claims asserted against us. We reviewed them in

our prior art papers and our experts are going talk about them. Let me just give you two examples.

Claims 2 and 10 of the '561 patent, they have indefiniteness problems. Why? All you do is read the claim. It is a composition claim. But then it has what appears to be a method step right in the middle, whereby said composition is used to form...

Now, here is the problem. Is this a composition claim or is this a method claim? And it makes a huge difference. Say I have two stock solutions that match up perfectly with this composition, one of which gets used in a patient but the other of which expires, so it never gets used in a patient. Does the one that I discarded because it expires, does it fall within the scope of this claim? If it is a composition claim, the answer would probably be yes, because it was designed to be used to form an injectable solution. So even though it was never used that way, if it is a composition claim you would probably say, yeah, it's probably covered. But if it is a method claim, it's clearly not covered. Why? Because it was never actually used to form an injectable solution. We threw it away. It expired. We never used it in a patient.

So we asked Sanofi's lead expert on this claim, on both infringement and invalidity, we said to him, I gave him the same type of hypothetical. And I said, is it

covered? And a lot of hemming and hawing, but in the end he said, I don't know. I don't know.

Well, that is the definition of indefiniteness. And actually this very issue was addressed in the Federal Circuit in '06 in the Amazon case, the very issue, the same issue.

Here is another problem: anaphylactic manifestations. This is all three asserted claims in the '561 patent.

Mr. Pappas said, well, let's look to the people in the front lines. We are bringing you somebody in the fronts lines. His name is Dr. Hilary Calvert. He is a renowned cancer physician. Been treating patients for 34 years. Why isn't he published? Extremely credentialed. He is going to come in here, he is going to say this phrase that is used in the patent, anaphylaxis manifestations, no set meaning at all.

During opening statements for Sanofi, they implicitly conceded this. Why? I am going to tell you why.

Continually, they talked about anaphylaxis. They kept saying this, anaphylaxis, anaphylaxis, anaphylaxis. That's not the term in the claim. The term in the claim is anaphylactic manifestations. And the symptoms for anaphylaxis are the same symptoms or they overlap with hypersensitivity reactions. There is no defined way to

distinguish between the two by just looking at their symptoms. It's, as Mr. Pappas said, I know it when I see it. When you say, "I know it when I see it," that means there is no good definition.

The key part really is -- and this is important under the case law -- Sanofi is using this phrase to try and distinguish the prior art from the claimed invention and the accused products and their own product. That phrase is supposed to help distinguish between the two.

They say Taxol caused anaphylactic manifestations, we don't cause anaphylactic manifestations. That's what they are saying.

Look at the real-world situation, Judge. Here is a black-box warning on Taxol, warning about hypersensitivity reactions. And guess what? There is a black-box warning on Sanofi's product, and there will be one in ours as well. They both require premedication to address hypersensitivity reactions, contrary to what I heard in the opening. They both have rare fatalities because of anaphylaxis. According to the labels, they both have two percent severe hypersensitivity reaction, two percent of the patients.

So what definition, what meaningful definition of anaphylactic manifestations somehow threads the needle between these two? I don't know how you would ever

construct such a definition. And that, I think, means the claim has to be indefinite.

Same thing with alcohol intoxication manifestations. They are trying to distinguish the prior art from what they say is the claimed invention. But how do you thread the needle? There was no issue in the prior art. And in terms of -- on an hourly basis the amount of ethanol that folks are getting is about the same, because in the prior art they gave the Taxol over a longer period of time.

So what definition of alcohol intoxication manifestations somehow threads the needle between the prior art and the alleged claimed invention? I submit I don't know how anybody would write a definition like that. I just don't. And I haven't heard one from Sanofi.

I am looking at my time, and moving on to noninfringement, Your Honor.

The '561 patent. It's consisting essentially of three ingredients.

The three ingredients are docetaxel, ethanol and polysorbate. We all know what "consisting essentially of" is designed to deal with. It is designed to deal with situations where somebody is essentially gaming the patent, where they add ingredients that are insignificant and have no material impact on the claimed product. That is not what is happening in this case, Your Honor. Hospira added two

ingredients: citric acid and PEG 300. And we did testing to determine, do they have an impact on our product, these two ingredients?

This is what you are going to hear from Julie Liu. She will be one of the people who will talk to you. She actually did this testing and supervised it. But Sanofi, who has the burden of proof in this case -- and we gave them our product, they had our product, we actually delivered it to a testing facility -- they are not coming before you with any testing results. None.

They may have done it, I don't know. But that's not going to be part of the their evidence in the case.

Here is what our testing showed, and this is not testing, critically, Judge, that we did during litigation. Just normal testing that we did during product development. Who would ever have known this was going to be in a courtroom in Wilmington, Delaware being shown to a federal judge someday? Nobody at the time.

They just did straightforward testing. They did accelerated stability tests. You may have heard about this in other cases. But basically it is four weeks, but at a really high temperature, like 50 degrees, they try to mimic normal stability.

So with citric acid and PEG, that active ingredient stays intact. You lose almost none of it.

Docetaxel, you lose almost none of it.

So what happens when you take out our two extra ingredients? It falls apart, docetaxel falls apart, down to 67 percent. That is a huge problem because that means this molecule, it doesn't disappear. It breaks apart and creates new chemical compounds that might be toxic to human beings, that might have unpredictable activities in human beings. The FDA would never, ever let you administer this version of the drug to a patient. They would never, ever let you do it.

So our two extra ingredients are the difference between success and failure. These are real ingredients that make a real difference, Your Honor.

That was our stock. And we also tested our perfusion. And this test was focused on: Does PEG 300 make a difference? Without PEG 300 the perfusion falls apart after about four and a half hours. With PEG 300 it lasts for six. That is a 33-percent improvement. These are real ingredients that make a real difference. Nobody is gaming the patents in this case.

Last point on consisting essentially of.

How did Sanofi get the consisting essentially of claims? Well, they distinguished a prior art product that matches up with our product in all material respects. Here is why.

They get confronted with this Tarr article you have heard about. This is the Yalkowsky article. It doesn't use Cremophor, by the way. So he didn't think it was essential. And he has 10 percent polysorbate 80, 30 percent ethanol, 60 percent pluronic. It is a three-solvent system. There are all three solvents. We have a three-solvent system, too. Polysorbate 80, ethanol, and PEG 300.

How does Sanofi get these consisting essentially of claims over the Tarr prior art three-solvent system? They say, hey, we claimed a two-solvent system. They say, that's what our claim is. And they say Tarr's extra ingredients, this pluronic, will materially affect the basic and novel characteristics of the claimed composition. That's what they told the Patent Office.

Why? Because there is no teaching or suggestion in Tarr that Tarr's composition would work when missing a component which makes up half its solvent base. Look at ours. That component makes up over half of our solvent base. So the same arguments they made to get their claim over Tarr apply to show that our product cannot possibly infringe these consisting essentially of claims, without anaphylactic manifestations, Claims 2, 5 and 10.

All you have to do is go right to the label. Here is what the claims instruct from the Court order. What

it means is you have to have a reasonable expectation of the product being injected without, without causing anaphylactic manifestation.

Here is the reality. Number one, Sanofi's product requires premedications to address hypersensitivity and so does ours. That is not in the patent anywhere. That alone tells you you are not avoiding it with the pharmaceutical formulation alone. You have to add something outsides of the claim. Moreover, both products are going to have black-box warnings -- they are the most severe warnings you can have on a pharmaceutical product -- warning of severe hypersensitivity and very rare fatal anaphylaxis.

Mr. Pappas misspoke. He said very rare "anaphylaxis." What is very rare is fatal anaphylaxis. People dying, that's rare. Anaphylaxis is less rare.

Here is the statistics. This is right from the label. This happens. Without premedications, 21 percent of the people who receive Taxotere had hypersensitivity reactions, 21 percent. 4.2 have severe hypersensitivity reactions. With three days of premedication -- because that is what you have to do to take Taxotere, you have to have premeds for three days before they will give it to you -- 15 percent still have hypersensitivity reactions, and 2.2 percent have severe.

That is just the reality, it happens.

Do we have a reasonable expectation when we give our product to thousands and thousands of people that we are somehow going to avoid anaphylactic manifestations when Sanofi failed to avoid them? We do not, Your Honor. On the contrary, it is pretty much guaranteed that when our product hits the marketplace, folks should experience anaphylaxis manifestations. And there is proper precautions that are taken. In fact, you have to have medical personnel on site and available watching you when it's first administered. So precautions are taken. But it will happen. We are not avoiding it. There is no reasonable expectation that we can avoid it. It will happen. Statistics will show that it will.

Last subject on infringement. This is the essentially free of ethanol.

Again, you got a stock solution and you got your perfusion.

Your ruling on the stock solution, I think it might have even been an agreed construction between the parties. A stock solution is essentially free of ethanol only if it has no more than 5 percent ethanol by volume.

What does our product have, our stock? 23 percent ethanol. That is over almost five times as much ethanol as is required to be essentially free of ethanol. Almost five times.

Taxotere itself, it's over the limit. It has 12 percent, Your Honor.

Here is a key point. They actually tried a product that was essentially free of ethanol, and it failed. It didn't work. This claimed invention removing ethanol, it actually failed and they had to put the ethanol back in. So now they have two and a half times the minimum limit there.

So nobody in this room is marketing products that are essentially free of ethanol under this patent.

How about for a perfusion? You know this is the dispute of over what your claim construction means that we talked about at our pretrial conference. It is the same amount of ethanol as a stock solution with no more than 5 percent ethanol by volume. You adopted our claim construction at the hearing with the modification that I personally suggested to avoid the argument that there was a process limitation.

And here is how at least I understood it at the time, Your Honor.

Look, this patent is worried about delivering too much ethanol to patients because they are worried about, they say, intoxication manifestations. That's what they say.

That wasn't a real problem. It truthfully was just an argument they made to try to get a patent, because

there was really never any problem with that issue. But that is the argument they made.

If a 23-percent stock has too much ethanol and then you use it to make a perfusion, the perfusion necessarily has too much ethanol as well. There can't be different answers on a perfusion versus a stock. Why?

Say you start with 4 milliliters in a stock. When you go over to the perfusion, you still have 4 milliliters. It doesn't change. If 4 milliliters is too much for the patient here, it's got to be too much here (indicating). Percentages change because you might do a fivefold dilution versus a 20-fold dilution. But it is always, under the claim construction, the same amount as the stock.

So we think it couldn't be any more straightforward than that. If the stock has too much, the perfusion has too much. There is a correlation between the two.

So what does Sanofi argue to get around this, Your Honor?

They are resurrecting the argument that got rejected at the Markman, but using different support. At the Markman they said perfusions are essentially free of ethanol, the meaning of the claims if it contains ethanol 2 percent by volume. That was their argument. And you

rejected it in a footnote. So now they are back here again. And I think the number I saw was 1.78 percent. So they changed it by that little degree.

And I have to admit, I wasn't really following the presentation on how they got to it. So this is derivative from the presentation I just heard. I took this from their expert reports.

But here is how they get to it, Judge. They say, when you said a stock solution, what you really meant is you used any hypothetical stock solution, any one you wanted.

So they went to the prior art, the '470 patent, they plucked an example out of the '470 patent, and said that's going to be the stock solution they use for the basis of a series of calculations which end up defining essentially free of ethanol and showing that we infringe.

A lot of problems with that. Number one is, that is a random, that is really a random starting place. The '470 patent that they used as the source, it's not discussed in the '512 patent. It is nowhere there. How can you construe a claim based on an example in a patent that is not even cited in the patent?

Another obvious problem is they start with a 5 percent stock solution for an infringement analysis but they ignore our 23 percent stock solution. Why are they starting

with a 5 percent when we have 23 percent with the calculations?

I don't think it makes a lot of sense.

Then they take the stock solution and ask to come up with dilution ratios. They have this calculation to come up with the dilution ratios, a calculation you will see nowhere in the '512 patent, nowhere in the prosecution history. It's something that they created from the '470 patent, which was not even cited.

Then, through that calculation, they come up with ratios for diluting this 5 percent stock solution that they identified as an example in this patent. And those dilution ratios, you are not going to see them in the '512 patent. They are nowhere in there. And they are not dilution ratios. They are trying to argue that we infringe by using dilution ratios that we do not use.

I can't do this argument justice, because I would first have to explain it really clearly and then try to untangle it. It would take me an hour. It's really that complicated. And it is not, I submit, an appropriate way to construe a simple term, essentially free of ethanol, in a claim. The way it should be construed is that simple, right there (indicating).

If the stock is too much, the perfusion is too much.

THE COURT: You really don't have to worry about making the argument at this point since these are openings. But go ahead.

MR. HURST: I am sorry. You are right. Fair enough.

I am just going to conclude right now. In the end, Your Honor, we don't think there is any invention here. This surfactant swap, it was disclosed at least three times before July of '91, including with docetaxel itself. And there is no infringement. In fact, we have a better product because we don't infringe. When we tried to follow the teachings -- that isn't why we did it -- but we actually used the formulation when the teachings of the patent failed. You saw that 67 percent number that I showed.

So the only reason we have a better product is because we do things like we add PEG 300, we add citric acid. We increase the ethanol nearly fivefold. And that's what enabled us to create the superior single, one vial of product.

Thank you, Your Honor.

THE COURT: Thank you, Mr. Hurst.

Apotex.

MR. DRESNER: Your Honor, may I distribute copies?

THE COURT: Please do, counsel.

MR. DRESNER: Your Honor, good morning.

THE COURT: Good morning.

MR. DRESNER: I am going to try and not repeat a lot of what you have already heard here. Suffice it to say that there will be some things similar with the Hospira presentation, and I ask that you bear with me on those similarities.

You have already heard a presentation regarding the history of this formulation. I am not going to repeat that.

I agree with what Mr. Hurst has said about this formulation, the subject of these claims not being an invention.

In 1991, to simply exchange polysorbate for Cremophor was not an invention. It was not something that should survive the patent process.

The challenge here is, and I ask you to keep this in mind as Mr. Hurst did, the challenge here is not to the drug docetaxel. As Mr. Hurst said, that is a great drug. It does save lives. The challenge here is to the formulation.

Just to keep in mind that the formulation here and the claims of the patent are directed to getting the drug docetaxel into that surfactant, polysorbate, so that it can be administered to a patient in a water environment in

an I.V. bag, the objective stated in the patent is to overcome the problems of the prior art, the Taxol drug that used Cremophor. But as Mr. Hurst said, that was not an invention.

The drug itself is covered by a patent already owned by Sanofi, the '470 patent.

We respect that patent, as does Hospira. We have filed what's called a Paragraph 3 certification, indicating we won't manufacture that until that patent expires.

What we have done instead in this case is file a Paragraph 4 certification, not an ANDA case, as Mr. Hurst said, but what's known as a (b)(2) application for a New Drug Application, simply because our formulation is different. It's not the same as the listed drug. It's a different formulation.

So our application is a (b)(2) application.

What I really want to do here, rather than repeating what you have heard about the prior art, is focus on the Apotex product and why that is different and why it's not covered by the claims.

The product that Apotex has described in its (b)(2) application and that they would hope to manufacture is different basically because the docetaxel drug itself is dissolved in PEG 300. This is unlike the situation in the

patents in suit, where the objective is to get docetaxel dissolved in the surfactant polysorbate.

By using PEG 300, the Apotex proposed product can further reduce the amount of ethanol in the formulation than if PEG 300 were not being used.

This is not to be confused with understanding whether or not the formulations that Apotex's products produce meet the claim limitation of free or essentially free of ethanol.

The fact of the matter is, we do bring down the amount of ethanol. And that has significant advantages. Ethanol, as you will hear, is a material that tends to degrade the active ingredient docetaxel. With less of it, you get less degradation and maintain chemical stability.

Adding PEG also results, as Mr. Hurst has indicated, in what's known as a three-part or ternary co-solvent system. This is something quite distinct from what's covered in the patents at issue, and it was distinguished during prosecution.

Sanofi uses ethanol because it's helpful to dissolve the docetaxel. But PEG 300, the use of PEG 300 in creating a three-part solvent system replaces an amount of ethanol and results in these advantages.

This creates an entirely different system. And, in fact, the manner in which these products are produced,

Your Honor -- you will forgive the colors, they are used just for illustration. This is not what these materials actually look like.

But in the process for producing the product described in the Apotex application, the docetaxel is dissolved directly in PEG 300. Once it's dissolved, and the application says it's completely dissolved, it stays dissolved. It doesn't get re-dissolved. It gets diluted when you add additional materials to it. But it's dissolved in PEG 300.

What happens in the Sanofi product instead is that the docetaxel is dissolved in ethanol. The polysorbate is added. The ethanol is driven off. And what you wind up with is a stock solution with docetaxel dissolved in polysorbate.

So as distinguished from the Sanofi product, the product that Apotex has described is something where docetaxel in the stock solution is dissolved in PEG, not in polysorbate.

The concentrated solution, the one that is produced by dissolving docetaxel in PEG 300 and not in polysorbate, in fact, is not the product that Sanofi is charging with infringement. It can't be because it doesn't include polysorbate. And that's a requirement of all the claims.

So we are not being charged with direct infringement, if you will.

Rather, the assertion here is that when you take this concentrated solution of docetaxel and PEG 300, and then when you combine it, when you combine it with another vial that Apotex will provide that does contain polysorbate, ethanol and water, when you mix them together, which is what the clinicians at a hospital will do prior to administration to a patient, that it's either that dilution, or when you take that mixture and further dilute it into the I.V. bag, it's those dilutions, those formulations or compositions that will infringe the claims: in effect, indirect infringement.

So in addition to having the burden to show that those dilutions infringe the claims, Sanofi has the added burden to establish that Apotex had the requisite intent, the requisite knowledge, for such indirect infringement.

So when the second vial, the one that I just described that contains the polysorbate, the ethanol, and the water, what we call a diluent is added to the first vial, what we wind up with is this three-part solvent system. And the drug remains dissolved. It doesn't get dissolved again in polysorbate. It's been dissolved in PEG 300. And, as Mr. Hurst indicated, this combination of docetaxel in polysorbate or in a combination of polysorbate

and ethanol was already known in the prior art.

Their own patent, the '470 patent, which covers the basic drug, the good drug, that already describes docetaxel. And the reference that you have heard a lot about and you will hear more about, the GV reference, describes the combination, a formulation intended for administration to humans of polysorbate and ethanol with the very drug in this case, Taxotere or docetaxel.

Let's take a look specifically at the claims of the patent and the Apotex product.

Claim 7 requires docetaxel, the active ingredient, dissolved in polysorbate, and, again, this expression, "essentially free or free of ethanol."

As I've indicated, the first vial, the concentrate that Apotex intends to produce, does not contain polysorbate so that is not being charged with infringement.

The second vial, that doesn't contain any docetaxel as required by this claim, so that is not being charged with infringement.

Your Honor has, as has been indicated, construed the expression, "essentially free or free of ethanol," and I'm not going to go over that analysis again. Mr. Hurst did it. He did it very well.

I agree with his explanation that for perfusion, the amount of ethanol that is allowed to be in that

perfusion to be essentially free or free of ethanol must be correlated with the accused product, not some hypothetical or prior art product.

So with that understanding, if we look at the downstream diluted compositions that are made with the Apotex product, not the first vial, because that has no polysorbate, not the second vial because that has no docetaxel, and even not the combination of those two which they are mixed to form a first dilution, because the record will indicate and the evidence will show that that has more than the required maximum of five percent, but rather let's talk about the final dilution perfusion, whether or not that can meet the requirement of "essentially free or free of ethanol." And we will show that it does not.

The original stock solution, the one that was in the first vial, that had no ethanol, it was purely docetaxel and PEG 300. So because the requirement for the perfusion to meet the limitation is that the perfusion have the same amount of ethanol, as Mr. Hurst described, this perfusion can't meet that requirement because the original stock solution had no ethanol. So the same amount is not in the perfusion because we've added ethanol.

So let's take a look at where the perfusion comes from. That is the first dilution, by mixing those two vials together. That has six percent ethanol in it. We've

added ethanol.

But that is more than the stock solution requirement of five percent. So if it's more in this first dilution, then it has to be more in the perfusion. So the limitation of five percent from the stock solution is exceeded and you can't have the same amount in the perfusion and meet the limitation. So for that reason, we do not meet the requirement of essentially free of ethanol.

There is another reason regarding non-infringement of Claim 7. And, again, I'll just simply emphasize that the claim requires docetaxel be dissolved in polysorbate. We dissolved it in PEG.

So for these reasons, Claim 7 does not infringe.

Let's take a look at Claim 33. Claim 33 is directed to a stock solution. And Your Honor has construed the expression, a "stock solution" to mean a concentrated solution. And we have no argument with that. We agree with that.

Again, the requirement of the claim is that docetaxel is dissolved in polysorbate. And for the same reasons that we spoke about Claim 7 not being infringed for that reason, this claim can't be infringed either.

There is an issue here as to whether or not that first dilution, the one that is created by mixing the first two vials together, is in fact a stock solution.

As I've said, we have no argument with Your Honor's construction of the expression stock solution being a concentrated solution.

The fact of the matter is that that first dilution, by mixing those two vials together, is a diluted solution. Is it more concentrated than the perfusion? Yes. It's a relative term. It is more concentrated than the perfusion. But is it otherwise a stock solution? That first dilution is intended merely as an intermediate stage to get the drug into the IV bag.

A person of ordinary skill in the art understands a stock solution to mean something that is maintained for future use. The use of that intermediate dilution is immediate. The product that Apotex has described is known as what is a single use product. In other words, the two vials are intended to be a single administration. It's not intended to mix those two vials together, put it on the shelf, use it once, put it back, take it back out again. It's a single use administration.

So we have a problem with this first dilution being considered a stock solution, and for that reason also, we don't think the claim is infringed.

So let's take a look at the '561 patent. And we're moving along, Your Honor.

Mr. Hurst described some problems with

definiteness expressions in the claims. This is another one. Claim 5 contains a limitation regarding the amount of ethanol and the amount of polysorbate. It says, which contains less than. Literally read, it's definite. It's clear on its face. "Less than" is less than and can include none. Zero is certainly less than.

If you read it that way, the prior patent owned by Sanofi, the docetaxel patent, directly anticipates that claim.

It contains the active ingredient with ethanol but no polysorbate. Literally read, it will anticipate that claim.

You will hear from the experts for Sanofi that there has got to be some amount of ethanol and some amount of polysorbate in the claim just to make it work, because, after all, that is their invention. Their invention is the use of polysorbate with some ethanol.

So what amount is that? The only example in the specification that indicates an amount of polysorbate and ethanol other than 35 milliliters per litter is one example that indicates 33 milliliters. Where is the lower limit that is required to make this composition work and achieve the functional objective of being capable of being injected without anaphylactic manifestations?

I submit a person of ordinary skill in the art

would not have enough information from the specification to figure out where those limits are. And without those limits, this claim is indefinite.

That's a summary of what I just said.

Mr. Hurst spoke about the limitation relating to, "without anaphylactic or alcohol intoxication manifestations." I'm not going to repeat it. You heard it. It's applicable to our product, just as the Hospira product. Your Honor has construed that expression, and I'm not going to repeat that story in the interest of time. So Claim 5 for those reasons is not infringed.

Moving on to Claims 2 and 10, these claims are quite similar, actually. These are the consisting essentially of claims, and this brings about the story of the basic and novel properties and whether or not the additional ingredients affect those basic and novel properties.

And this is your Court, Your Honor's construction "consisting essentially of" and we know what that means.

The addition of PEG 300 does indeed affect the basic and novel properties of these claimed inventions. We've pointed out already that it decreases the ethanol, and that is a significant advantage.

You have heard the story from Mr. Hurst about

the two co-solvent system, and it bears some repetition, Your Honor, at least briefly. And that is that during the prosecution of the applications that led to this patent, the applicant said to the Patent Office, in order to obtain their patent and distinguish their invention from the Tarr reference, that their invention consists essentially of a two-part solvent system, a significant distinguishing feature over the reference.

That reference contained, as Mr. Hurst said, pluronic L64 consisting 60 percent of the solvent system, a considerable percentage. Not too different than the almost 50 percent or slightly less of PEG 300 that is in the Apotex product. So they can't have it both ways. They can't have it one way to get the patent and another way in litigation.

There is one more feature about these claims that I'd like to comment about. Mr. Hurst indicated the indefiniteness of the expression, formed or to form an injectable solution. Even if it were not to be indefinite, the Apotex product would not meet that limitation. The requirement of the claim is that it's the mixture of docetaxel with ethanol and polysorbate that is used to form the injectable solution.

The product that Apotex has described in its (b)(2) application is a mixture of docetaxel, ethanol and polysorbate 80 and PEG, a different combination. That is

what forms the injectable solution. So, again, this claim, and, therefore, none of the claims, are infringed.

Let me address just a couple of other issues relating to invalidity and inequitable conduct. We have a double patenting issue in this case. Double patenting, as Your Honor may know, is a concept that is intended to prevent two patents from claiming the same inventive entity.

We have a situation here where two of the claims in the '512 patent claim the same inventions as in the '582 patent. This is a problem that frankly is easily avoidable during prosecution or even afterwards. An owner of a patent can file what is called a terminal disclaimer. You effectively give up the term of the patent of the later patent that is longer than the term of the first patent. And you acknowledge that you will own both patents. You will continue to own both patents.

As a simple matter of fact, no terminal disclaimer exists in the history of the '512 patent. You will hear Sanofi say that they executed a terminal disclaimer. They submitted it to the Patent Office. But the truth of the matter is the Patent Office hasn't accepted it. I'm frankly not sure why, but there is no terminal disclaimer. And that, as a matter of law, renders these patents, or at least the '512 patent, invalid.

One final point, Your Honor. And that is on

inequitable conduct. Mr. Hurst mentioned it briefly. And you heard about the GV reference. You are going to hear more about it. The GV reference is not only a basis for invalidating the patents, because they, as Mr. Hurst said, spilled the beans, they disclosed the formula, and therefore it's so relevant to the prosecution or would have been so relevant to the prosecution, but, in fact, the applicants knew about it, and they used it in their internal documents. They used itself in their bibliography. They submitted it to the FDA in their investigative brochure. So when it served their purpose to submit it to a government agency, they used it. But they did not submit it to the United States Patent Office, and they clearly should have.

So, Your Honor, for all those reasons, we believe the Apotex product does not infringe the claims, the claims are invalid over the prior art for the reasons Mr. Hurst described, they're invalid for double patenting, and they're unenforceable for inequitable conduct. Thank you for your time.

THE COURT: Thank you, counsel. Let's take a break.

(Brief recess taken.)

THE COURT: Please be seated. Mr. Pappas, your first witness.

MR. PAPPAS: Thank you, Your Honor. Plaintiffs

call Dr. Howard Burris.

Your Honor, I would like to introduce to the Court Robert Kajubi, who is here from Aventis, the company representative.

Also, Your Honor, we have some demonstrative slides we will use with Dr. Burris. I understand from talking to Mr. Aly there may be a couple of objections. And what I would suggest is we deal with those as we come to the slides, in context, if that is all right with Your Honor.

THE COURT: That's fine.

... HOWARD A. BURRIS, III, having been duly sworn as a witness, was examined and testified as follows ...

MR. PAPPAS: Your Honor, if I may, may I hand up copies? This way you will have a set as well.

THE COURT: Ms. Walker will be right with you, Mr. Pappas.

MR. PAPPAS: Very well. Thank you.

THE COURT: These are the demonstratives?

MR. PAPPAS: Yes, Your Honor. Your Honor, as we discussed in the pretrial conference, we have a notebook for you and for your law clerk of the exhibits that we have produced to the other side. We understand we are getting these back.

THE COURT: Yes, you will.

MR. PAPPAS: We are handing them up for use now during his examination.

THE COURT: That is fine. You can just hand them directly to Matthew Scherer there, and he will give me mine as well.

MR. PAPPAS: Thank you.

THE COURT: You may proceed, Mr. Pappas.

MR. PAPPAS: Thank you.

DIRECT EXAMINATION

BY MR. PAPPAS:

Q. **Dr. Burris, will you state your full name and address?**

A. **My name is Howard A. Burris, III. I reside at 18 Angel Trace (phonetic), Brentwood, Tennessee 37027.**

Q. **Dr. Burris, do you have a microphone up on the stand there?**

THE COURT: It will pick him up.

MR. PAPPAS: I want to be sure, Your Honor, he is speaking loudly enough to be picked up by the court reporters.

THE COURT: They will let you know.

MR. PAPPAS: Thank you, Your Honor.

BY MR. PAPPAS:

Q. **Are you a medical doctor, Dr. Burris?**

A. **Yes, I am.**

Q. **I want you to trace your educational background,**

beginning with your graduation from high school?

A. **I graduated from high school in 1977 in Montgomery, Alabama. Upon graduation, I matriculated to the United States Military Academy at West Point in 1977. I graduated from the United States Military Academy in 1981.**

Q. **And did you have a specialty or a major area of study while you were at West Point?**

A. **I did. I graduated with a Bachelor of Science degree and majored in chemistry.**

Q. **And since it's relevant to your ability then to go to medical school, where did you finish in your class at West Point?**

A. **I graduated approximately 30th in my class at West Point.**

Q. **Out of how many cadets?**

A. **Of 960 graduates.**

Q. **What did that enable you to do so upon your graduation and being commissioned as a Second Lieutenant in the United States Army?**

A. **Upon graduation, I was commissioned in the United States Army. By finishing in the top five percent of my class, I was eligible to go to graduate school. Near the time of graduation, I applied for and was accepted to medical school, and initiated that medical school in late that summer 1981.**

Q. **What medical school did you attend?**

A. **I attended the University of South Alabama in Mobile, Alabama.**

Q. **Did you graduate or receive your M.D. degree?**

A. **Yes, I did. I graduated from the University in May of 1985.**

Q. **What did you do upon your graduation from medical school?**

A. **Upon graduating from medical school, I was promoted to the rank of Captain in the United States Army, and assigned to Fort Sam Houston in San Antonio, Texas, where I initiated an internship at Brooke Army Medical Center.**

Q. **What was your internship in?**

A. **My internship was in internal medicine.**

Q. **When did you finish your residency?**

A. **I finished my medical residency, internship and residency, in 1988 there in San Antonio.**

Q. **What did you do upon completion of your internship and residency?**

A. **During my residency, I had become involved in cancer research, in the field of oncology. And I applied for and was accepted to a medical oncology fellowship there at Brooke Army Medical Center at the University of Texas Health Science Center in San Antonio, beginning in 1988.**

Q. **What is oncology?**

A. **Oncology is the study of the field of cancer.**

Q. **For how long did you serve this Fellowship?**

A. **I graduated from my Fellowship in June 1991.**

Q. **What did you do upon finishing your Fellowship?**

A. **Upon finishing my Fellowship in 1991, I was promoted to the rank of Major in the United States Army. And at that time I became a staff physician there at Brooke Army Medical Center, as well as an assistant professor at the University of Texas Health Science Center at San Antonio.**

Q. **What did you do at the University of Texas Health Science Center?**

A. **I was initially the associate director of clinical research for the Institute of Drug Development. I also served as an adjunct faculty. I was in charge of teaching residents and Fellows, primarily in the field of drug development.**

Q. **For how long were you there?**

A. **I remained in San Antonio, both in my position in the Army and at the University, until the summer of 1997, until July of 1997.**

Q. **At what school did you teach?**

A. **The school was the University of Texas Health Science Center at San Antonio.**

Q. **What did you teach?**

A. **I taught oncology. I taught clinical research in the**

field of medical oncology.

Q. **Did you practice medicine the entire time you were in the Army?**

A. **I practiced medicine continuously. I practiced oncology until being called up for deployment in the fall of 1996.**

Q. **Were you deployed?**

A. **I was deployed in October 1996 with the first Cavalry Division to Operation Joint Endeavor in Bosnia.**

Q. **What did you do in Bosnia?**

A. **In Bosnia I served as the Chief Medical Officer for Combat Support Hospital in association with the First Cavalry Division, supporting our troops who were deployed throughout that theater.**

Q. **How long were you there?**

A. **I was there for a little over six months, finishing in April of 2007.**

Q. **Where did you return to upon leaving Bosnia?**

A. **I returned back to Fort Sam Houston, back to Brooke Army Medical Center.**

Q. **Did there come a time when you resigned your commission and were honorably discharged from the United States Army?**

A. **I did. Upon return, I was promoted to -- I went to Bosnia, actually, promotable to Lieutenant Colonel. Upon**

returning, I was officially promoted to Lieutenant Colonel, and shortly thereafter resigned my commission and was honorably discharged from the U.S. Army.

Q. **In what year?**

A. **That was in 1997.**

Q. **What did you do upon your discharge from the Army?**

A. **Upon my discharge from the Army, I joined Tennessee Oncology, a private oncology group, and the Sarah Cannon Cancer Center, a research facility, in Nashville, Tennessee.**

Q. **Did you have a specialty practice in Tennessee?**

A. **I did. In addition to seeing patients that had cancer, I also was the director of the drug development program. I ran the Phase I and early Phase II clinical research program.**

Q. **Right now you used a term Phase I and Phase II clinical programs. Can you explain briefly what Phase I clinical programs are and what Phase II clinical programs are and how they differ?**

A. **Phase I clinical programs are the initial testing in humans, in patients. Phase I is a series of clinical trials that's aimed at determining the best dose and best schedule as well as the safety profile of in this case cancer drugs.**

Upon determining appropriate safety and the best schedule, those drugs are then moved into Phase II testing, where they are then tested against a more homogeneous group

of patients, a group of patients with breast cancer, for example, lung cancer, all contained within one diagnosis.

Q. **Are you still a member of the Tennessee Oncology practice?**

A. **I am. I still practice with Tennessee Oncology. I joined in 1997, became a partner in 1999, and serve on the board of Tennessee Oncology still today practicing medicine internationally.**

Q. **Can you estimate for the Court approximately how many cancer patients you have seen in your career at Tennessee Oncology?**

A. **Since coming to Tennessee Oncology, my average volume is to see between 200 and 250 new patients a year. So during the last 12 years, more than 2000, a few thousand more than that considering the time since the beginning of my Fellowship.**

Q. **And is there a distinction between new cancer patients and other level of care that you have given to patients suffering from cancer?**

A. **Yes. In addition to seeing new patients and new consultations, I also see patients that participate in our clinical trial program. I have other investigators that work with me. And being the head of the program, I tend to meet with, oversee, and review the cases of the other patients participating in the clinical trial program.**

That is another fairly large group of patients that I have become involved with secondarily.

Also, I see patients that have been diagnosed with cancer, previously treated, and now have failed their standard therapies or the disease has progressed through those standard therapies and they have been referred in port clinical trials. So they already have a preexisting diagnosis.

Q. **Do you have any other employment other than with Tennessee Oncology since you left the Army?**

A. **I do. The Sarah Cannon Cancer Center has evolved as an institute now known as the Sarah Cannon Research Institute. I have been the chief medical officer of the Sarah Cannon Research Institute since August 1st, 2006.**

Q. **What do your duties and responsibilities involve as the chief medical officer of the Sarah Cannon Research Institute?**

A. **At the Sarah Cannon Research Institute, I am the senior physician for oversight of the other physicians as well as our clinical trial program. I directly report to the chief executive officer. I am involved in some of the business aspects, with the licensure of physicians, as well as overseeing the conduct and care of all aspects of the clinical trial program, including the data, regulatory and other aspects.**

Q. **Is the Sarah Cannon Research Institute, I take it that is involved with oncology, with cancer?**

A. **Yes. Our primary focus is cancer research, more than 90 percent of our research is involved in cancer and cancer drugs in particular. It is strictly a clinical research program. We have no laboratory testing there.**

We treat more than 3000 patients a year on clinical trials from a range of Phase I, Phase II and Phase III.

Q. **And we have covered already what Phase I and Phase II studies are.**

Can you tell us what Phase III studies are that you have been responsible for at the Sarah Cannon Research Institute?

A. **So Phase I, as I mentioned, was to determine the safety, best dose, and schedule. Phase II is really quite simply to understand if the drug works in cancer patients and how well it works. And assuming there is sufficient activity seen, a Phase III trial would be to compare that agent, either in combination or against the standard therapy for that disease.**

Q. **Now, do you have any other titles with the Sarah Cannon Research Institute in addition to being the chief medical officer?**

A. **So I am the chief medical officer there as well as the**

director of the Drug Development Program at Sarah Cannon.

Q. **What do you do as head director of the Drug Development Program?**

A. **The Drug Development Program is a portion of our overall research program. It is in my area of clinical expertise. We treat about 500 patients a year in Phase I trials. It is one of the larger programs in the United States.**

I have a team of physicians that I supervise, as well as a team of additional 50 staff that provide research nurses, clinical nurses and pharmacists that specialize in treating patients with Phase I investigational agents.

Q. **Turning now for a moment to the issue of clinical trial research, what does the term principal investigator mean?**

A. **The principal investigator is a physician designated with a clinical trial program to be the lead physician, and they resume and assume the investigative responsibilities set forth by several agencies. The Food & Drug Administration has a Form 1572 which outlines quite clearly the responsibilities of the principal investigator, to assure that the protocol, that the research is conducted in compliance with an improved protocol and that both the appropriate safety standards are maintained. Additionally, the principal investigator is accountable to the**

Institutional Review Board, which oversees making sure that the patients are appropriately consented for participation in the clinical trial.

Q. **Have you served as a principal investigator before in Phase I trials?**

A. **Yes, I have.**

Q. **Can you tell us approximately how many times you have been the principal investigator on a drug being studied in Phase I?**

A. **I have been the principal investigator on more than 200 individual Phase I clinical trials during my career.**

Q. **How many of those have been cancer drugs?**

A. **All of those have been cancer drugs.**

Q. **Does the term first-in-man trials mean anything to you?**

A. **Yes, it does.**

Q. **What does it mean and what does it refer to?**

A. **Within the context of Phase I trials, as one can imagine, there would be several different schedules explored, several different administration techniques and several trials.**

The first-in-human or first-in-man trial is a center or investigator selected to deliver the very first dose to a patient. That is something that we had an area of expertise in while I was in San Antonio. And I carried that

to Nashville. In my career I have been the principal investigator on more than 70 first-in-man trials, including more than 60 since my time in Nashville.

Q. Can you estimate for us and for the Court how many new cancer drugs you have been involved in the investigation of, from a clinical perspective?

A. So I have been involved in the study and with development of more than 200 different anticancer agents.

Q. Now, are you retained -- is the Sarah Cannon Research Institute asked to do this by various companies, specifically, pharmaceutical companies who have drugs under study?

A. Yes. Our primary response, our primary contract partners are pharmaceutical and biotech companies.

Q. Have you done work -- has Sarah Cannon Research Institute done work before for sanofi-aventis?

A. Yes, we have.

MR. PAPPAS: Rather than, Your Honor, go through every pharmaceutical company, let me just ask the question this way.

BY MR. PAPPAS:

Q. With all the clinical trials you have done in the cancer area at the Sarah Cannon Research Institute, is there any pharmaceutical company in America that has not hired the Sarah Cannon Research Institute to do clinical trials?

A. **I am not aware of a pharmaceutical company in the United States doing cancer research that we have not worked with.**

Q. **Let me ask you to turn in your binder to Joint Trial Exhibit 245, in your notebook, it is a system we lawyers use, Joint Trial Exhibit will be designated as JTX. I ask you if you could turn to that, please?**

Dr. Burris, let me just ask you to state, if you can, for the record, is this a copy of your curriculum vitae?

A. **Yes, it is.**

Q. **Does it contain the various articles and abstracts that you have written on chemotherapy treatments, including Taxol and Taxotere?**

A. **Yes, it does.**

Q. **Let me turn now to Taxol and Taxotere particularly that we are here about today. For how long have you had any involvement with the drug Taxol that has the molecule in it paclitaxel?**

A. **I became involved with the drug Taxol during my residency in 1987. So more than 20 years.**

Q. **And what was the occasion under which you first became involved with Taxol?**

A. **I was a medical resident and associated with an investigator on a clinical trials program at the University**

of Texas, at the Brooke Army Medical Center where senior oncologists were conducting clinical trials.

Q. And have you had experience with Taxol after its clinical trials when it was ultimately approved for sale or for prescription?

A. Yes. Since the approval of Taxol in December 1992, I've been involved with using the product off-study in the context of treating patients as part of my practice continuously since 1992 as well as being involved in a number of clinical research programs that involve Taxol during the 90s.

Q. Have you prescribed, as a physician, Taxol for the use and treatment of patients suffering from cancer?

A. Yes, I have.

Q. Now, have you had contact or experience with Taxol uninterruptedly since it was first approved by the FDA?

A. Yes, I have.

Q. Now, let's turn to Taxotere. What was your first involvement with what came to be known at the Taxotere formulation?

Q. My initial involvement with Taxotere known as RP56976 at that time was participation as the principal investigator on the first Phase I trial conducted in the United States?

A. And were there other sites where clinical trials, specifically Phase I, were being performed on Taxotere?

A. **Yes, there were three sites that participated in Europe and two in the United States: the University of Texas and the Brooke Army Medical Center as well as M.D. Anderson.**

Q. **Did you actually administer Taxotere to any of the patients in the Phase I clinical trials?**

A. **Yes, I did.**

Q. **Were you the first doctor to administer Taxotere to any patient in the United States?**

A. **Yes, I was.**

Q. **And was that the second dose administered anywhere worldwide, the first being in Paris?**

A. **Yes, it was. As you mentioned, the initial dose was given with Professor Marty of Paris, France.**

Q. **Have you worked with Taxotere since its approval by the FDA in 1996?**

A. **Yes, I've worked with Taxotere continuously actually since the early research days as well as since its approval.**

Q. **And what phases of clinical trials did you participate in as a principal investigator for the formulation that came to be known as Taxotere?**

A. **I participated in additional Phase I trials of Taxotere as we looked at it in combinations of other drugs.**

I also participated with Taxotere during its Phase II testing in breast cancer, lung cancer and prostate

cancer, and then also participated in the Phase III program that was eventually compared with the other standard drugs against a variety of other diseases.

Q. **Have you had contact and experience with the formulation Taxotere literally from when it became studied under clinical trials, Phase I, all the way through its clinical trials, up to, and including, the present day?**

A. **Yes, I have.**

Q. **Can you estimate for the Court approximately how many patients you have treated with Taxotere in your career?**

A. **Taxotere is widely utilized and has a number of FDA applications. It's not uncommon for a quarter or a third of my patients who are receiving Taxotere for the various indications. So that number is certainly greater than 1,000 patients.**

Q. **Are you charging for the time you are spending as an expert witness in this case?**

A. **Yes, I am.**

Q. **At what rate?**

A. **$500 an hour.**

Q. **And are you getting paid for your services or is that money going elsewhere?**

A. **No. That money, as part of our policy, that money goes to the Sarah Cannon Research Institute.**

Q. **Dr. Burris, do you consider yourself an expert in**

clinical aspects and consequences of chemotherapy formulations, including a specific expertise in prescribing and administering Taxol and Taxotere?

A. **Yes, I do.**

Q. **Do you consider yourself an expert in the clinical testing and development of chemotherapy formulations, including Taxotere?**

A. **Yes, I do.**

MR. PAPPAS: Your Honor, based on Dr. Burris's education training and experience, we would proffer him as an expert to the Court in the areas of clinical aspects and consequences of chemotherapy formulations, including specific expertise in Taxol and Taxotere, and also an expert in the clinical testing and development of chemotherapy developments, including Taxotere.

THE COURT: Any objection?

MR. ALY: No, Your Honor.

MR. DRESNER: No objection.

THE COURT: The Court will accept the doctor as an expert in the areas.

MR. PAPPAS: Thank you, Your Honor.

BY MR. PAPPAS:

Q. **Dr. Burris, I'd like to turn your attention to a very brief description of cancer, since that is what we're here about. What is cancer in its most general sense?**

A. **So cancer is the disease that describes a condition where a cell, the cancer cell grows uncontrollably, divides without dying, and has the ability to spread to other organs in the body or metastasize.**

Q. **And, approximately, how many different types of cancer are there?**

A. **Cancer, once subdivided by the organ in which it originates, and then looking at the different cell types within those organs, some quote there are as many as 200 forms of cancer that are actually possible for a patient or a human.**

Q. **And do these cancers present different or the same treatment challenges?**

A. **They present different, unique treatment challenges.**

Q. **And, typically, what is the form of treatment of these various cancers in terms of general modalities?**

A. **So the three general modalities upon which we approach treating cancer are surgical options, options that involve radiation therapy, and then chemotherapeutic options.**

Q. **And then does the term "combination therapy" have meaning to you as an oncologist?**

A. **Yes, it does.**

Q. **What does it mean to employ combination therapy in the treatment of cancer?**

A. **So, the most common application for the term**

"combination therapy" is to think about combination chemotherapy, giving more than one drug together, giving drugs that have different side effect profiles and different means of killing the cancer cells so one can gain an even greater advantage in trying to eradicate the cell.

Also, combination therapy is sometimes utilized when they talk about giving lower doses of chemotherapy in combination with radiation therapy to try to eradicate a tumor.

Q. Are there combinations where you prescribe two or more drugs in what is referred to as I guess a cocktail to treat the patient?

A. Correct. Cocktails are combination chemotherapy regimens that are actually the mainstay for most therapies for cancer patients, particularly patients where we are treating in the postsurgical setting where you are trying to eradicate or potentially cure the patient of their disease.

Q. Now, with that being true, what, if anything, is important about how those two or three drugs may coexist in the human body?

A. So several important factors with those. When you start adding more than one drug into a combination, there are concerns about side effects, you know, making sure we don't see overlapping side effects. That we don't see potentiation of side effects.

That also gets into thinking about the pharmacology of those drugs and thinking about drug interactions, making sure you are getting predictable side effects and efficacy profiles in the administration of those drugs together.

Q. **I want to turn other attention to the first taxane, Taxol; all right? Are you with me?**

A. **Yes, I am.**

Q. **Do you know when the National Cancer Institute first selected Taxol or specifically the molecule paclitaxel for clinical development?**

A. **Yes. It was in 1977.**

Q. **And at that time, were there any taxane formulations approved anywhere, to your knowledge, for the treatment of cancer?**

A. **No, there were not.**

Q. **In terms of the general state of affairs of cancer agents, where did taxanes fit then in 1977?**

A. **So in 1977, the taxanes as a class were being studied in preclinical models, in laboratory models. There was an excitement and enthusiasm at that time, as I read about and was educated about by my mentors. Just the promise of a new drug.**

Q. **And are taxanes as a class -- let's be specific here. Paclitaxel and docetaxel, which found its way into the**

formulation of Taxotere, did they present any challenges at all to formulators?

MR. ALY: Objection, Your Honor. Lacks foundation. The question was about formulators.

THE COURT: Yes, it was.

MR. PAPPAS: Yes, Your Honor. I can lay a foundation for that.

THE COURT: If you can, go ahead.

BY MR. PAPPAS:

Q. **Will you describe your experience in formulation of drugs used to give patients the treatment for cancer?**

A. **So my experience comes from, as a clinician, working with formulators in terms of looking at those aspects of drug delivery systems and solutions that need to be formulated and which they can be safe and reasonably efficaciously given to our cancer patients.**

Q. **And in your practice not only as an oncologist but as a clinical trial Phase I, II, III investigator, did you have occasion to come into contact, to deal with issues having to do with the way drugs are formulated?**

A. **Yes, I did.**

Q. **And how so?**

MR. ALY: Objection, Your Honor. Lack of foundation as an expertise. Dr. Burris is not offered as a formulation expert.

THE COURT: Yes. I think you can rephrase your original question, Mr. Pappas. He was not offered as an expert in formulations. Why try to elicit a response from him that is geared to that expertise. And I'm sure he has expertise in formulations, there is no doubt, as a clinician, that he would.

MR. PAPPAS: Yes.

THE COURT: But you are going to have formulators testify, aren't you?

MR. PAPPAS: Yes, Your Honor.

THE COURT: Okay.

MR. PAPPAS: I can rephrase the question I think in a way that would avoid the objection.

THE COURT: Sustained.

BY MR. PAPPAS:

Q. **Dr. Burris, are there any particular issues or problems that you have become aware of in your career, as a clinician and an oncologist, with taxane formulations as it applies to the clinical practice?**

A. **Yes. Taxanes, by reputation and by the data that was generated, are natural molecules. They come from the taxus species. The natural molecules are larger molecules. You get into formulations classified as not being water soluble, and they present challenges with solutions in which they are dissolved or in which they are formulated. Those**

formulations can sometimes have side effects in treating patients, and are certainly relevant to clinicians, medical oncologists in particular.

Q. **Are you concerned as a clinician with the side effects of medicines that you administer to patients?**

A. **Yes, I am.**

Q. **Is it part of your business, your profession and the oath you have taken as a physician to know and understand the side effects that are caused by the medications you prescribe on a daily basis?**

A. **Yes, it is.**

Q. **Do you make it your business on a regular daily basis to keep up with the research, to know, for instance, there are new side effects or new benefits with a formulation that you make a decision everyday to prescribe?**

A. **Yes, I do.**

Q. **In fact, do you teach others about this?**

A. **Yes, I do.**

Q. **Now, can you tell us when the clinical trials first began with the Taxol formulation?**

A. **The Phase I clinical trials with Taxol began in 1983.**

Q. **And how did you know this?**

A. **At that time, I was still in medical school. That was taught during our medical oncology -- during our residency on medical oncology fellowship in the mid to early '80s.**

Q. **And did you have occasion to learn what happened to the Taxol formulation as soon as, literally, quickly after it was put into Phase I trials?**

A. **Yes. My boss and mentor, Dr. Daniel Van Hoff at that time, was one of the investigators involved in the early Phase I clinical trials with Taxol.**

Q. **What did you come to learn about what happened at the clinical trials?**

A. **I learned that shortly after initiation of trials that there were allergic reactions noted, that in fact patients experienced anaphylaxis, that at least one patient died as a result of that anaphylaxis, and the clinical trials were halted. They were stopped.**

Q. **Was the suspension of the clinical trials of the formulation known as Taxol widely known and recognized in the literature?**

A. **Yes, it was. It was widely discussed at that time. And it was something that made, you know, quite a bit of news actually throughout the medical community.**

Q. **Now, before we go any further, doctor, you used the term "anaphylaxis." And there is certainly going to be a substantial amount of debate in this case about it. I want to ask you, first, does the term "anaphylaxis" have a well established meaning in the medical community and particularly those that teach oncology?**

A. **Yes, it does.**

Q. **Can you tell what it is, based on your education, training and experience?**

A. **Anaphylaxis is a Grade 4 allergic reaction. A Grade 4 reaction in the description of anaphylaxis is one which is life threatening, one which requires lifesaving immediate intervention, often associated with, and usually consisting of, collapse of the vascular system, patient's blood pressure being unresponsive, and the patient often losing consciousness.**

Q. **Is this a condition that comes on over a long period of time or quickly?**

A. **It comes on very quickly.**

Q. **Are you trained to recognize it?**

A. **Yes, I am.**

Q. **Are you trained to treat it?**

A. **Yes, I am.**

Q. **Are all doctors that work with cancer patients trained to recognize it?**

A. **Yes, they are.**

Q. **And trained to treat it?**

A. **Yes, they are.**

Q. **What happens if you don't treat it?**

A. **If you don't treat it, and if you don't treat it immediately, the patient can die.**

Q. **Is that well known among the physicians?**
A. **Yes, it is.**
Q. **Are you trained to recognize it?**
A. **Yes, I am.**
Q. **Do you know the symptoms when you see it?**
A. **Yes, I do.**
Q. **What I am trying to understand here, doctor, in view of the opposition's ideas about some kind of hypersensitivity reactions when a patient goes into anaphylaxis, do you have time to call for a second or third opinion?**
A. **Actually, no. And there are degrees of allergic and hypersensitivity reaction, but anaphylaxis is a unique condition, described as a shock-like condition, requiring immediate and lifesaving interventions.**
Q. **And what role do nurses play?**
A. **As one would expect, often, the nurse is the one that is there at the bedside or the chemotherapy chair when the reaction starts. Those nurses are trained in cardiopulmonary resuscitation. They usually recognize, and particularly oncology and chemotherapy nurses recognize, the anaphylaxis and initiate treatment upon recognizing the condition.**
Q. **Are the nurses trained to recognize anaphylaxis?**
A. **Yes, they do.**
Q. **Do they, in fact, recognize it?**

A. **Yes, they do.**

Q. **Do they know how to treat it?**

A. **Yes, they do.**

Q. **Are they trained how to treat it?**

A. **Yes, it's an important part of their training.**

Q. **Now, have you ever witnessed any deaths due to anaphylaxis?**

A. **Yes, I have.**

Q. **On your watch?**

A. **Yes.**

Q. **And what were the patients taking?**

A. **I've had two patients expire from receiving a Taxol injection, anaphylaxis, there in the clinic, and one patient receiving cetuximab.**

THE COURT: Do we have a glossary of terms for our court reporters? Maybe counsel can work on it.

MR. PAPPAS: I can certainly work on that, get that together for our court reporters.

BY MR. PAPPAS:

Q. **Dr. Burris, is there an established common toxicity criteria which investigators use to classify various allergic events?**

A. **Yes, there is. The National Cancer Institute puts forth criteria that has been updated through the years known as the CTC, the Common Toxicity Criteria.**

Q. **Can I ask you to take a look at what is in your notebook as Plaintiff's Trial Exhibit 722?**

A. **(Witness complies.) Thank you.**

MR. ALY: Your Honor, I know that this binder has been presented to me. I just don't know if this is a version of the CTC that Dr. Burris relied upon during the expert reports and, therefore, cannot cross-examine him on this version of this chart. As you may see, Your Honor, there are versions that change.

THE COURT: Counsel, I'm aware of that, but I'm sure that given Mr. Pappas's experience, he is going to establish that.

MR. PAPPAS: Oh, yes. There is no doubt he had this.

THE COURT: We can save some time if you don't interpose frivolous objections.

MR. ALY: I agree.

THE COURT: Okay.

BY MR. PAPPAS:

Q. **First of all, let's establish what Plaintiff's Trial Exhibit 722 is. Can you tell us what this is?**

A. **Yes. This is Page 1 of 4 of the NCI, Common Toxicity Criteria, Version 1.**

Q. **All right. And when was this in effect?**

A. **This was in effect from the mid-80s through the 90s.**

Q. **And is this referred to in one of your many expert reports?**

A. **Yes, it is.**

Q. **All right. In fact, do you recall Mr. Aly questioning you about that at your deposition?**

A. **Yes, I do.**

Q. **And comparing it to a later version?**

A. **Yes.**

Q. **So he has been through this.**

MR. ALY: Your Honor, I just want to clarify. This is Version 3. Mr. Pappas may have made a mistake.

THE COURT: Version 3.

MR. ALY: Version 3 and Version 1. The record should be clear, the two versions he had considered were Version 3 and Version 4, and this is Version 1.

THE COURT: This is Version 1.

MR. ALY: Version 1, which was not on his report. That was the basis of my objection. I'm sorry, I phrased it differently.

THE COURT: Mr. Pappas.

BY MR. PAPPAS:

Q. **Is there any difference between 1, 3 and 4 with respect to anaphylaxis being a Grade 4 reaction?**

A. **No. The Common Toxicity Criteria of Version 1 was used during the clinical trials with Taxol and Taxotere**

during the Phase I, Phase II development. The criteria for anaphylaxis Grade 4 were consistent with Version 1, Version 2, Version 3.

THE COURT: Counsel, you will have a chance to cross-examine him about it, so why don't you sit down.

BY MR. PAPPAS:

Q. Now, let me direct your attention to the line entitled Allergy.

MR. PAPPAS: And can we have that highlighted, Dave? Thank you.

BY MR. PAPPAS:

Q. Can you explain this toxicity criteria that comes from the National Cancer Institute just with relation to the allergy line and the various grades, Dr. Burris?

A. So, quickly, the category is listed as allergy. The toxicity is allergy. Some of the others are subdivided. Grade zero is obviously one that did not occur and not listed here. Actually, Grade 5 is where somebody has a fatal outcome. Grades 1, 2, 3, 4 describe. Grade 1 is a transient rash. Grade 2 would be urticiria, known as hives, maybe some mild wheezing. Grade 3 would be serum sickness, also described as chills. Bronchospasm, which is wheezing. And at this point, one might receive medication. They might receive some antihistamines. And then Grade 4 is anaphylaxis, a unique condition with shock-like symptoms.

Q. **In your opinion, are physicians trained to recognize the difference between the grades of these reactions?**

A. **Yes. Actually, they're fairly clear. Certainly, Grade 4 is a much more dramatic life threatening toxicity.**

Q. **Now, I have another question. If I were to use the word "anaphylactic symptoms," would that have a meaning to a physician?**

A. **Yes.**

Q. **And in order to have anaphylactic symptoms, what would I have?**

A. **So if you are having symptoms of -- anaphylactic symptoms would be symptoms of anaphylaxis. The patient was, you were concerned the patient was having anaphylaxis, moving into shock-like symptoms.**

Q. **Now, let's change the question slightly. Let's say that I called you in distress and told you my wife had anaphylactic manifestations. What would you conclude as a physician that I was describing?**

A. **My concern would be that you were describing a Grade 4, a shock-like life threatening condition, manifestations of anaphylaxis.**

Q. **Do you have an opinion whether a physician would use anaphylactic manifestations to refer to transient rash?**

A. **They would not.**

Q. **Would they refer to it as drug fever?**

A. **No, they would not.**

Q. **Would they use it to refer to serum sickness under Grade 3?**

A. **No, they would not.**

THE COURT: Doctor, are you saying that they are equivalent terms?

THE WITNESS: I am saying that, yes, the term "anaphylactic manifestations" or "anaphylaxis" would be synonymous for a physician.

BY MR. PAPPAS:

Q. **Now, once the trial's clinical Phase I trials of Taxol were halted, what was the next step?**

A. **The clinical trials were halted, and there was a great deal of discussion about steps to take obviously with the development of a new cancer drug that was thought to hold some promise. There is a great deal of discussion among researchers, publications, and meetings discussing what steps might be able to be taken to enable us to get a drug like this, to give Taxol to patients.**

Q. **Was there any consideration given to switching from Cremophor to polysorbate 80 when Bristol-Myers Squibb, National Cancer Institute realized they had a problem?**

MR. ALY: Objection. Lack of foundation, Your Honor.

THE COURT: It's also leading as well.

MR. ALY: And leading.

MR. PAPPAS: That was leading, Your Honor.

THE COURT: Sustained.

BY MR. PAPPAS:

Q. **Do you have any knowledge --**

A. **So the knowledge --**

Q. **Just a minute. Let me finish my question. Thank you.**

Do you have any knowledge of whether or not any alternatives to Cremophor were discussed when the trials were halted?

A. **Yes, I do.**

Q. **Okay. What is the basis of that knowledge?**

A. **The basis of that knowledge is my own readings, discussions and lectures at that time and discussions in particular with my mentor, Dr. Von Hoff, in San Antonio.**

Q. **Who is Dr. Von Hoff?**

A. **Dr. Von Hoff was the Director of the Institute For Drug Development there. He was the lead Phase I, senior Phase I investigator there in San Antonio. He was an internationally recognized expert in Phase I research and one of the investigators on the Taxol program.**

Q. **And what did you learn from that?**

A. **I learned from Dr. Von Hoff that, what ended up being developed, there was several formulations attempts, several looks at what possibly could be switched to looking at some**

of the data that had been evaluated from the National Cancer Institute, that other formulations were not felt to be suitable for Taxol, and Cremophor was felt to be essential for its activity.

Q. Was there any discussion at that time of what was causing the anaphylactic shock that was being experienced in Phase I trials?

A. There was discussions being held as to whether it was the Cremophor, whether it was the natural product or the taxane. And the feeling was that it was more than likely, if not almost certainly, that Cremophor largely contributed, if not solely contributed, to the development of the anaphylaxis.

Q. Now, as part of those discussions, was there any mention of simply switching out Cremophor and putting in polysorbate 80?

MR. ALY: Objection, Your Honor. Discussions he is referring to that are with mentor Dr. Von Hoff is not a form -- this is a formulation question put to the doctor.

THE COURT: Please rephrase the question. I need to hear it again.

MR. PAPPAS: Sure. I am happy to, Your Honor.

BY MR. PAPPAS:

Q. In terms of the discussions that were going on with Dr. Von Hoff -- who was a Phase I clinical investigator for

Taxol; correct?

A. **Correct.**

Q. **Was there any discussion of the formulation of Taxol -- which was paclitaxel and Cremophor; correct?**

A. **Correct.**

Q. **Was there any discussion of simply taking the Cremophor out of the formulation used on patients and putting polysorbate 80 in its place and restarting the Phase I trials?**

MR. ALY: I object, Your Honor. Dr. Von Hoff's communication was not in his expert report. It's beyond the scope. And it is a formulation question.

THE COURT: Well, it's not a formulation question, per se, but you are saying it's not in his expert report?

MR. ALY: That is also true.

MR. PAPPAS: Your Honor, I think this is strictly part of history. It's part of his -- he has his ultimate opinions, but I'm giving the foundation for his opinions.

THE COURT: I'll allow it. Go ahead.

THE WITNESS: There was discussions about utilizing other such formulations, such as polyethylene glycol, polysorbate, but they were not felt to be suitable due to the decreased activity of Taxol as was reported over

that time with the formulation.

BY MR. PAPPAS:

Q. **Let me ask you this: Did there come a time when the Phase I trials were allowed to proceed?**

A. **Yes, there was.**

Q. **And are you familiar with the conditions that allowed the Phase I trials of Taxol to proceed?**

A. **Yes, I was.**

Q. **And what were they?**

A. **So there were three discussions held at that time that changed the formulation which was not felt to be appropriate or suitable. There was a discussion about lengthening the infusion of the drug, so that's protracting the infusion out to a longer period of time, and then there was discussion about adding in premedication drugs such as steroid or antihistamines to try to block the allergic reaction.**

Q. **Was that ultimately adopted as a condition for going forward with the Taxol drug?**

A. **Yes. In fact, in the interest of safety, the investigator at that time decided to take both steps. They increased the duration of the infusion to 24 hours and they added on an aggressive premedication regimen utilizing steroid and antihistamines.**

Q. **How did the patient receive Taxol if the infusion was 24 hours long?**

A. **So patients would come into the clinic, see us, and then be admitted to the hospital where they would receive the infusion overnight under a hospitalized condition.**

Q. **And the premedication that you have described before the patient was administered Taxol, my question now is how is that premedication administered?**

A. **So the premedications administered beginning at least 12 hours before the dose with an oral dose of a steroid dexamethazone was commonly used. Then a period of six to eight hours before the infusion, receiving a second dose. Then upon coming into the clinic, approximately an hour before initiating the infusion, patients were treated with IV premedications which also then included antihistamines, what we would call an H1, H2 blockers, putting together both a diphenhydramine, or Benadryl, and cimetidine, or Tagamet, so we combine a block of antihistamines and steroids.**

Q. **Now, as these Phase I trials were proceeding, was there nevertheless a search for an alternative formulation for Cremophor?**

MR. ALY: Objection, Your Honor. Again, it's a formulation question outside the scope.

THE COURT: Overruled. Overruled.

THE WITNESS: Yes. There continued to be searches for unique formulations for the taxanes, and that continues today.

BY MR. PAPPAS:

Q. **Can you turn in your binder to the Plaintiff's Exhibit 553?**

A. **Yes.**

Q. **I believe this was referred to in your rebuttal expert report at 24 and 35.**

A. **Yes.**

Q. **Do you recognize this article?**

A. **Yes, I do.**

Q. **And what is it titled?**

A. **The title of the article, it's a Phase I trial of Taxol given as a three-hour infusion every 21 days.**

Q. **Can you explain to the Court how we went from 24 hours to three hours with Taxol?**

A. **Well, this was one of the initial trials. This was one of the trials that actually resulted in halting the studies. This was one of the initial reports. So it was after this trial that, in fact, the infusions were lengthened to 24 hours.**

Q. **Are you familiar with Dr. Kris or any of the authors listed on that article?**

A. **Yes. Actually, Dr. Kris is somewhat of a mentor and certainly a colleague for the last few years and also one of the investigators at Sloan-Kettering Cancer Center.**

I have also had a chance to work with Dr.

O'Connell, Gralla and Young.

Q. **How would you describe the reputations of these men in the oncology community as practicing physicians?**

A. **This is a group of physicians from Memorial Sloan-Kettering and Cornell University. They are widely regarded as experts in oncology and highly respected for their work in the field.**

Q. **The date on this article, at least as to when it was actually published, Dr. Burris, is what?**

A. **Is May 1986.**

Q. **Let me direct your attention to the last paragraph that appears on Page 607 of the article, but with these Bates numbering systems that lawyers use in these cases, it bears a number at the bottom, Hospira 43895. Do you see that?**

A. **I do.**

Q. **That paragraph, can you read it, and tell us what is disclosed there?**

A. **So here Dr. Kris writes that, "Hypersensitivity reactions constitute a severe and unpredictable treatment-limiting toxicity for the present Cremaphor-containing formulation of Taxol given on this schedule. Further studies are needed to see if pretreatment regimens, alternative schedules, or a reformulated preparation will permit the safe administration of this**

compound."

Q. **What is he telling us there?**

A. **He is telling us that it is unsafe to give the Taxol as it was being conducted in their clinical trials, as a three hour infusion without premedication.**

Q. **Was Dr. Kris involved in the Phase I trials?**

A. **Yes. He was the actual principal investigator on this study at Memorial Sloan-Kettering.**

Q. **Was the patient who died his patient?**

A. **Yes.**

Q. **The reference in that paragraph to looking for a reformulated preparation, my question to you, sir, is was that the conventional thinking in 1986, that they needed to find something other than Cremophor?**

A. **Yes.**

THE COURT: Mr. Pappas, we will break for an hour.

(Luncheon recess taken.)

THE COURT: Please be seated. Let's resume.

MR. PAPPAS: Thank you, Your Honor.

BY MR. PAPPAS:

Q. **Dr. Burris --**

MR. PAPPAS: May I proceed, Your Honor?

THE COURT: Certainly.

MR. PAPPAS: Thank you.

BY MR. PAPPAS:

Q. **Dr. Burris, before the luncheon recess, I believe you had just finished with the Kris article that discussed the attempt to find another formulation.**

MR. PAPPAS: Can I have that back on the screen, Dave, please? Thanks.

This is Plaintiffs' Exhibit 553, the last page of the article.

If you will highlight that last paragraph, please.

Q. **Now, Dr. Burris, can you tell us whether or not even after the Phase I trials of Taxol continued, whether or not medical experts continued to search for an alternate formulation without Cremophor?**

A. **Yes, they did.**

Q. **Now, before I go to that, how was the -- can you tell us how the revised regimen for administering Taxol was viewed in the medical community? By that I mean the extended premedication period up to -- premedication plus four-hour infusion? How was that perceived?**

A. **It was perceived as being cumbersome.**

Q. **Let me ask you to take a look at Joint Trial Exhibit 283, please. I believe in preparation of your report you reviewed this patent. Is that correct?**

A. **Yes, I did.**

Q. **Let me direct your attention, by the way, so we are clear what is the title of this patent?**

A. **The title of this patent is Methods for Administration of Taxol.**

Q. **Who is the assignee of the patent?**

A. **Bristol-Myers Squibb.**

Q. **Is this the same Bristol-Myers Squibb that was involved in the development of Taxol?**

A. **Yes, it was.**

Q. **Let me ask you to direct your attention to Column 3, Line 36 through 42.**

Can you highlight that for us, Dave?

Can you indicate and testify to the Court what is being disclosed there by Bristol-Myers Squibb about the revised treatment regimen of Taxol?

A. **It describes the fact that you can minimize the side effects by use of a long infusion. That infusion duration is inconvenient, that it's expensive because you are monitoring the patients during a hospitalization. And it requires the patients to spend an overnight stay.**

Q. **Just so we are clear, this is the Bristol-Myers Squibb who developed Taxol?**

A. **Yes.**

Q. **Is that statement by Bristol-Myers Squibb, the developer of Taxol, do you have an opinion as to whether or**

not that was a widely held consensus view of physicians involved in treating cancer patients at that time?

A. **Yes, it was the consensus for medical oncologists at that time.**

Q. **I would like to move forward now to the question I asked you several moments ago about continued efforts to develop a Cremophor-free formulation. Why was anybody trying to do that?**

A. **The two reasons were, there was excitement about some of the antitumor activity seen with Taxol, and then the biggest concern was the anaphylaxis, the life-threatening reactions the patients were experiencing, which made it of great concern for administering in the clinical, eliminating the Cremophor was thought to be the best solution for that.**

Q. **But, as we have just covered, if Bristol-Myers Squibb had extended the infusion time and was giving corticosteroids and antihistamines and they restarted the trials, why did anybody care about still trying to replace Cremophor?**

A. **The longer duration of infusion and the installation of an aggressive premedication regimen reduced the incidence of the anaphylactic and anaphylaxis that was observed but it did not eliminate it. So there was still a desire to come up with a better product.**

Q. **At any time prior to 1991, when the patents in this**

case were filed, had anybody developed a suitable substitute for Cremophor in the Taxol formulation?

MR. ALY: Objection, Your Honor. Lacks foundation and it's outside the scope of the expert report.

MR. PAPPAS: Your Honor, it is in his opposition report at Page 66.

MR. ALY: Your Honor, we thought invalidity was something in our case. Obviously, he can establish secondary considerations. But when he is establishing these kinds of considerations it purely goes to the obviousness or nonobviousness of the patents.

MR. PAPPAS: When we discussed the order with the parties, it was our understanding that we would discuss objective nonobviousness on the validity question. After all, we had the burden of proof in our case and we had the burden of going forward with our experts in the case in the first instance on the objective indicia of nonobvious. This would fall into this category of failed attempts.

What we agreed with Mr. Hurst is that the traditional validity challenge of our response to their combinations and anticipation argument would go second. And in the words of Mr. Hurst, he said that way Mr. Pappas and Mr. Sipes would know what to shoot at.

Well, as we agreed -- and we can have the pretrial transcript -- we covered the objective indicia of

nonobviousness, commercial success, failure of others, where we have the evidence. And then Mr. Hurst an Mr. Aly will know what to respond to in their case.

That is what we are doing now. And at Burris Opposition Report Page 66, this was covered. The specific article that I want to show him.

THE COURT: Mr. Hurst, is that your understanding?

MR. HURST: The answer is yes, that is our understanding.

THE COURT: Then overruled.

BY MR. PAPPAS:

Q. **Let me ask you to direct your attention, Dr. Burris, to Joint Trial Exhibit 145.**

Do you recognize this article, sir?

A. **Yes, I do.**

Q. **What is the title of it?**

A. **Hypersensitivity Reactions from Taxol.**

Q. **When was it published?**

A. **This article was published in July 1990.**

Q. **In what journal?**

A. **Published in the Journal of Clinical Oncology.**

Q. **Is that a respected journal?**

A. **Yes, that is a peer-reviewed journal.**

Q. **And this is by Raymond Weiss and others?**

A. **Yes.**

Q. **Do you know any of the gentlemen listed there as the authors?**

A. **Yes. I know of and have met all of the authors. Several of the authors were colleagues, or probably more appropriately stated, mentors of mine.**

Q. **Well, I notice one in particular, Daniel D. Von Hoff. My question, sir, is this gentleman any relation to the Dr. Von Hoff you testified about before lunch?**

A. **Yes. This is the same. This is Dr. Dan Von Hoff, who was the leader of the program in San Antonio.**

Q. **Let me ask you to direct your attention to the column that starts on the bottom of Page 44784 and goes over to 44785. You have at least the paragraph up here, one on top of the other. So we get it in context it starts with, If Cremophor EL.**

In the lower right-hand corner, 44784?

Then the completion of that paragraph, Dave, at the top of 44785.

All right. Dr. Burris, what does Dr. Weiss say, your former mentor Dr. Van Hoff and others, tell us there?

A. **They are stating there that if Cremophor EL is a suspected initiator of reactions from Taxol, could some substitute excipient be used that would be less apt to cause HSRs? Polyethylene glycol has been tried as a substitute,**

but this chemical appeared to decrease the antitumor activity of taxol in murine tumor studies. At present, there is no suitable substitute for Cremophor EL in Taxol formulation.

Q. **Do you agree with that?**

A. **Yes, I do.**

Q. **Do you have an opinion as to whether or not that was the consensus of oncologists in the medical community as of 1990, that no one had been able to find a suitable substitute for Cremophor in Taxol formulation?**

A. **Yes, it was.**

Q. **Had doctors been trying to find a substitute?**

A. **Doctors had been requesting, certainly medical oncologists were desirous of having a different formulation, a different excipient to have in the Taxol product. And we were told by researchers, Bristol-Myers Squibb and the National Cancer Institute, that that was not possible. That this was the -- the current Cremophor EL was the best to go with.**

Q. **That was from Bristol-Myers Squibb or the creator and developer of Taxol?**

A. **Yes.**

Q. **Then finally, let me ask you to turn to Plaintiffs' Trial Exhibit 209. Have you seen this article before?**

A. **Yes, I have.**

Q. **What is the title of it?**

A. **Role of Formulation Vehicles in Taxane Pharmacology.**

Q. **Do you recognize any of the authors there?**

A. **Yes, I recognize all the authors.**

Q. **Is one of them Dr. Alex Sparreboom?**

A. **Yes.**

Q. **Let me ask you to direct your attention to Page 135 of the article, which bears the Bates number Hospira 105335. Specifically, in the left-hand column, the words begin, Notwithstanding these observations, through to in vivo antitumor activity.**

What is Dr. Sparreboom referring to there, sir? Before we go there, I note the date of this article is 2001. Correct?

A. **Correct.**

Q. **What is he commenting on there, he and the other authors in the highlighted portion?**

A. **Commenting on the fact that it was noted in early studies conducted by the National Cancer Institute that paclitaxel or Taxol was not effective in tumor models when it was given as a solution in polyethylene glycol 400 or 10 to 15 percent Tween 80-ethanol, which would be polysorbate 80, suggesting that the Cremaphor-based vehicle was essential for the in vivo antitumor activity.**

Q. **Was that the prevailing view of the medical community**

as of that time in the early studies?

A. **Yes. It was widely accepted that in fact the Cremophor was an important component of the activity of the compound.**

Q. **Were you here for the opening statements, Dr. Burris?**

A. **Yes, I was.**

Q. **Did you hear the statement by, I believe it was Mr. Hurst, that Dr. Sparreboom was mistaken and didn't understand the article that the author cited to?**

A. **Yes.**

Q. **Do you agree with that?**

A. **I do not.**

Q. **Now, before I pass from Taxol, is Taxol still given today for some cancer patients?**

A. **Yes, it is.**

Q. **Is premedication with glucocorticosteroids and antihistamines intravenously still required?**

A. **Yes, it is.**

Q. **And what is the infusion time now? 24 hours or less?**

A. **With the use of the more aggressive premedication regimen, we have reduced the infusion for standard doses of Taxol down to three hours.**

Q. **Does the term crash cart mean anything to you? By that I mean in the medical context?**

A. **Yes.**

Q. **What does the crash cart mean to an oncologist?**

A. **A crash cart is a small table with multiple drawers in it. They usually need that. Now we have in the chemotherapy clinic and in the hospitals where these therapies are delivered, on the top of a crash cart is a defibrillator capable of restarting the heart, and then within the drawers of the crash cart contain various medicines and devices that assist in intubating a patient or providing life-saving medications, medications such as epinephrine or adrenalin, other medications that might be helpful in restarting the heart or supporting the blood pressure.**

Q. **What is the status of the crash cart today in hospitals where you practice where Taxol is administered?**

A. **So the crash cart is still kept within the clinics, still kept near the bedside for the patient that develops anaphylaxis when receiving a Taxol infusion.**

Q. **Is anaphylaxis still an issue with the administration of Taxol even today with the premedication and the infusion period?**

A. **Yes, it is.**

Q. **Let me ask you to turn your attention to Plaintiff's Trial Exhibit 444.**

Have you seen this before?

A. **Yes, I have.**

Q. **What is the title of it?**

A. **Cremophor EL Containing Paclitaxel Induced Anaphylaxis: A Call to Action.**

Q. **Where is the published?**

A. **This is published in Community Oncology.**

Q. **When?**

A. **It was published in March of 2009.**

Q. **Are you familiar with any of the authors?**

A. **Yes, I am.**

Q. **When one?**

A. **The senior author, Charles Bennett, from the University of Illinois-Chicago, is a colleague of mine and someone that I have known for years.**

Q. **All right. Let me ask you to direct your attention to Page 133. It bears Bates number SA1005149. And, specifically, the middle column and the sentence that begins with the word "however" and finishes with the country name "Japan."**

Okay. Now, as of March 2009, what are the authors reporting?

A. **These authors were reporting that fatalities occurred in 22 percent of the reported cases, referring to paclitaxel associated anaphylaxis despite the use of premedication prophylaxis. Another important finding of this work is poor quality adverse event reporting is not unique to the U.S.**

Equally poor adverse event reports were submitted to the regulatory agencies in Europe and Japan.

Q. **What is the significance of that?**

A. **The significance is the regulators were stating we still have patients dying from paclitaxel or Taxol-induced anaphylaxis. And they still believe, based on the case reports and the use, that in fact this is likely to be underreported and the reports are insufficient in equality and quantity.**

Q. **Just so we're clear. On the 22 percent, is this 22 percent of all patients who get Taxol or are they reporting of the patients that get anaphylaxis on Taxol, we lose 22 percent of them?**

A. **So they're stating here that in the 96 cases that are reported in this publication, that of those 96, 22 passed away. And the inference in reading the article and somewhat suggested is certainly with the use of Taxol and with the use of the crash cart, with the use of the nurses being there and with the lifesaving medications that we use, that, in fact, a majority of the patients are saved and don't die from having anaphylaxis. So that is part of their methodology for suggesting this is widely underreported and not represented of the number that truly occur.**

Q. **All right. Let's turn to Taxotere. What was your role in the Phase I testing of the formulation of docetaxel,**

polysorbate 80 and ethanol that came to be known as Taxotere?

A. **So in the late summer, early fall of 1990, we initiated trials in San Antonio with RP56976, which was the docetaxel formulation preparation at that time. I was the principal investigator at the site in San Antonio. It was a trial looking at it once every three week infusion of the RP56976 docetaxel. There was four trials in addition to mine that were on going, one in Houston at M.D. Anderson and three in Europe.**

Q. **Did the Taxotere Phase I trials have to be halted at any of the five sites?**

A. **No, they did not.**

Q. **What can you tell the Court about whether or not anaphylaxis was observed in the Phase I clinical trials upon the administration of the formulation?**

A. **So, in the conduct of my trial, our trial in San Antonio, we saw no cases of anaphylaxis through the 40 plus patients that we treated. And all those patients were treated without premedications.**

For the database of the more than term 50 patients that were enrolled in these five trials and that the investigator meetings and subsequent manuscripts, there was no cases of anaphylaxis reported. And those trials were also administered without premedication.

Q. **All right. Is there a way we can -- was there data kept of what happened at the other sites of the Phase I clinical trials other than San Antonio where you were?**

A. **Yes, there was several mechanisms. Obviously, in conducting the trial, the investigators spoke and there was frequent investigator meetings. And then ultimately when the trials were completed, there was an Integrated Safety Summary performed that pooled all the data for all the trials together in addition to the individual publications that were made.**

Q. **Is that a standard practice at the end of clinical trials, to pool all the data in what is called a document called an Integrated Safety Summary?**

A. **Yes, it is.**

Q. **All right. Can you turn to Joint Trial Exhibit 69 in your binder, and tell us if that is the Integrated Safety Summary on the Phase I and Phase II clinical trials formulation that was used?**

A. **Yes, it is.**

Q. **All right. Let me ask you to turn to Page -- I'm going to use the Bates numbers now again, Dr. Burris. It's the easier way to keep track -- 91577.**

Are you there, sir?

A. **Yes, I am.**

Q. **Okay. Can you tell us what this page represents?**

A. **So this is Table 12, which is an overall analysis of docetaxel related nonhematologic toxicity.**

Q. **What is nonhematologic toxicity as opposed to hemologic toxicity?**

A. **So we tend to classify, subdivide oncology clinical trial toxicities into two categories: hematologic and nonhematologic. Hematologic focused on lowering white blood counts, lowering red blood counts or anemia, lowering platelets. The blood cells are commonly affected by chemotherapeutics. The nonhematologic toxicities are other organ toxicities, for instance, alopecia or hair loss, also toxicity that would affect the GI tract, the heart and other organs.**

Q. **All right. Is there a portion -- oh. And before we go down to allergies, what are the three categories that actually descend vertically with data but are listed horizontally?**

A. **So the overall incidents which would encompass Grades 1, 2, 3, 4 toxicities and then subdividing the more severe toxicities, we tend to want to see Grade 3 and Grade 4 reported separately.**

Q. **Okay. Now, I know we covered it before lunch, but what is being referred to there in this chart by the designation Grade 3 or Grade 4?**

A. **So Grade 3, or those toxicities by the NCI Version 1,**

Common Toxicity Criteria, was provided with the protocol of a score of toxicities.

Q. **And I believe we looked at that this morning. That was Plaintiff's Exhibit 722, I believe.**

A. **Yes, that is correct.**

MR. PAPPAS: All right. Dave, if we can scroll down.

BY MR. PAPPAS:

Q. **Is there a line on this chart that would have captured whether or not there was any anaphylaxis suffered by the patients in the Phase I trials?**

A. **Yes. Listed about two-thirds of the way down is a line that has got the initials, AHSR. In parentheses besides that, allergy.**

Q. **What does that reflect?**

A. **So these are the allergic reactions that were experienced. AHSR stands for acute hypersensitivity reactions. They report an overall incidence in 40 of the patients.**

Q. **And how many patients total?**

A. **So there were 255 patients in this compilation. 15.7 percent was the overall incidents. And then they report 7 of these were Grade 3 or 2.7 percent. Zero cases of anaphylaxis or Grade 4 toxicity was reported.**

Q. **All right. And did any of these 255 patients receive**

premedication?

A. No, none of the patients in these received premedication.

Q. And is this chart or table of Phase I or Phase II?

A. This is from the Phase I trials.

Q. All right. Let me ask you to direct your attention to Page 91625.

And what is shown there, sir?

A. This is Table 43B. These are the nonhematologic toxicities. They're similar to the table we reviewed. It was 100 milligrams per milliliter squared of docetaxel, possibly or probably related to the treatment worst grade by patient, also no premedication. So these are from the Phase II trials which were conducted 100 milligram per milliliter squared, and this is what the investigator said it was likely to be related to the study medication.

Q. And is there any line on there which captures the incidents of allergic reactions and, specifically, whether or not there was any anaphylaxis suffered by any of the patients?

A. Yes. About two-thirds of the way down, the top chart here, we also see the designation AHSR. The subtitle there, acute hypersensitivity reactions. And then again the number of patients in the Phase II trial was 415. The overall incidents reported was 36 or 11.4 percent of the patients.

21 of those listed as Grade 1 or mild. Grade 2 were 9 patients. Grade 3 were 3 patents. And there were no patients listed as Grade 4 or anaphylaxis.

Q. **Now, let me ask you to turn to Page 91624, which happens to be the immediately prior to page.**

And can you tell us what that chart reports?

A. **Yes. This chart, Table 43A, same category, classifications, nonhematologic toxicities. Again, a dose of 100 milligrams per milliliter squared of docetaxel, possibly or probably related to the treatment worst grade by patient overall. And this included some of the patients who received premedications.**

Q. **All right. Is there any line that reflects whether or not there was any incidence of Grade 4 anaphylaxis?**

A. **There are. There are designation twos-thirds of the way down. Again, AHSR for acute hypersensitivity reaction.**

Q. **And how many patients total?**

A. **So of the 830-plus patients listed here, the overall incidents, 31.3 percent. 200 patients -- 260 patients listed there. 262. The overall grade, 103 of those patients is Grade 1, 59 is Grade 2, 56 is Grade 3, and 5 is Grade 4.**

Q. **And is it 5 out of 837 for Grade 4?**

A. **Yes.**

Q. **As if my math is correct, that's about .06 percent?**

A. **Yes.**

Q. **Now, did you have occasion to examine the study results and take a look at the symptomology reported by the five patients that were reported as Grade 4 anaphylaxis?**

A. **Yes, I did, actually.**

Q. **And what did you find?**

A. **I found that of those five cases, none actually met the definition of what investigators or medical oncologists would consider anaphylaxis. In fact, three of those cases were contained within the study report from a non-small cell lung cancer, a lung cancer trial on which I was an investigator.**

Q. **Can you explain that?**

A. **Yes. You know, in looking at those three cases in particular, the most interesting finding that would make me think that they were not anaphylaxis was the fact that the infusion was stopped, the patients were supported, and then the infusion was reinstituted during that same visit.**

In the setting of true anaphylaxis, and the patient having a life threatening condition in which you would institute lifesaving measures associated with shock, vascular collapse, it would seem to be highly unlikely and improbable that someone would restart the offending agent.

Q. **All right. Does it happen from time to time in recording the data that mistakes are made?**

A. **Yes. I mean it could be that mistakes are made and then sometimes it isn't the physician. Sometimes there is a data manager and the adjectives or adverbs use the term "toxicities" to get graded subjectively as opposed to the person actually taking care of the patient.**

Q. **Now, did there come a time when Taxotere was approved for sale in prescription in the United States?**

A. **Yes, it was approved in 1996.**

Q. **All right. Now, is there any premedication that sometimes is given to patients who are going to take Taxotere?**

A. **Yes, there is.**

Q. **And what kind of premedication was that?**

A. **The patients receive three days of oral steroids as the standard premedication to be used, although there has been research to cut that back further as well.**

Q. **And for what condition are those steroids given?**

A. **Those steroids are given strictly for the condition of fluid retention or edema that those patients taking docetaxel for longer period of time can experience.**

Q. **And can you contrast for us the nature and extent of the condition of edema as a potential issue with paclitaxel and anaphylaxis with Taxol?**

THE COURT: The edema with Taxotere, the edema with this agent is what I would consider more of a nuisance

toxicity. Interestingly, it occurs with patients doing well with their therapy. It tends to come after five, six or more courses with the drug. So these are patients that have been on the drug therapy five or six months or longer and are clinically benefitting. And there is a small percentage of patients that will develop fluid retention or edema.

The use of premedications from the outset with the use of Taxotere has been shown to reduce the incidence and severity of the fluid retention.

Q. **How does that compare, the medical condition, anaphylaxis with Taxol?**

A. **So it is a nuance toxicity that occurs gradually, is not life threatening, and is often fairly easily managed with supportive medications such as a diuretic or water pill, stark contrast and not at all in the realm of anaphylaxis, which is key to immediate life threatening and occurs shortly after initiating infusion and requires a life saving intervention to take place.**

Q. **All right. Dr. Burris, I now want to move after the approval or to the formulation of Taxotere. In addition to the benefit of avoiding anaphylaxis and required premedication, do you have an opinion as to whether or not the formulation known as Taxotere exhibited unexpected benefits?**

A. **Yes, I do.**

Q. **And what were they?**

A. **The unexpected benefits that we, as investigators, medical oncologists, researchers saw with the use of Taxotere are listed on this slide.**

MR. PAPPAS: Your Honor, I've had Plaintiff's Demonstrative Exhibit 2-2, for the record, put up.

BY MR. PAPPAS:

Q. **Please continue.**

A. **And in helping to prepare this document, listed here are some of the key factors:**

The polysorbate 80 clears the bloodstream much faster, which has found to be an unexpected benefit.

There is linear pharmacokinetics for this Taxotere formulation which is certainly an unexpected benefit.

And we have reduced clinical side effects, reduced drug to drug interactions.

We have less neuropathy.

And not listed here but shouldn't be understated is the fact we can deliver Taxotere as a simple one hour infusion once every three weeks, so a short infusion on an infrequent schedule.

Q. **Are these unexpected benefits related to the polysorbate 80 in the formulation?**

MR. ALY: Objection, Your Honor. There is no foundation for this and it's outside the scope specifically of that one ingredient.

MR. PAPPAS: Your Honor, it is very much within the scope. That is what he testified to before. Defendants have made an issue in their opening statements that these unexpected benefits or these benefits are the result of the docetaxel molecule, having nothing to do with polysorbate 80, and thereby attempt to trivialize the formulation of polysorbate 80.

The questions I am asking now, what Dr. Burris has been establishing is that these unexpected benefits stem from the formulation and specifically in his opinion stem from the use of polysorbate 80.

MR. ALY: Your Honor, it's okay to talk about these secondary considerations. But that question I object to because it asks about one variable, polysorbate 80. There is no opinion on that, no tests that have been done. It is not a report on what this one ingredient could do different.

THE COURT: Sustained.

MR. PAPPAS: Your Honor, if I may, though, it has been covered in his report. The favorable dosing regimen was covered in his report, Page 69. The avoidance of drug interactions, at the rebuttal report at Page 25.

THE COURT: Let me get a reaction.

MR. ALY: Your Honor, I have no objection to any of those questions. But it has to be about Taxotere, not polysorbate 80. That was my basis for that objection.

THE COURT: It is a very narrow objection. And I am sustaining it, Mr. Pappas.

Are you disagreeing with what was covered?

MR. PAPPAS: Your Honor, I will ask it a different way.

BY MR. PAPPAS:

Q. **Do you have an opinion as to whether or not these unexpected benefits that you have just testified to, are they related to Taxotere?**

A. **Yes.**

Q. **Were any of these benefits that you have just listed on the slide a benefit of Taxol?**

A. **No.**

Q. **Now, Taxol uses Cremophor. Correct?**

A. **Correct.**

Q. **And Taxotere uses polysorbate 80. Correct?**

A. **Correct.**

Q. **Are you aware of any literature that says that those unexpected benefits are due to the docetaxel?**

A. **No.**

Q. **Are you aware of any literature that says those**

unexpected benefits are tied to polysorbate 80?

A. **Yes.**

Q. **Now, let me ask you to look at Plaintiffs' Exhibit 214, please. Do you have this document, sir?**

A. **Yes, I do.**

Q. **Have you seen it before?**

A. **Yes, I have.**

Q. **What is it?**

A. **This is a letter to the editor, written by a group of authors from three different institutions, commenting on some recent publications and data presented in this journal.**

Q. **Can you enlighten us a bit on this practice of physicians writing letters to the editor in physicians' journals?**

A. **Yes. This is a journal Clinical Pharmacology & Therapeutics. Much of what is written in this journal often pertains to oncology drugs.**

This is a group of investigators that have all published separately within this journal, and have come together to write a letter that synthesizes together and confirms the various reports that have been made in much longer publications. So a letter for the readers to be able synthesize that information and make their points jointly.

Q. **Let me ask you to direct your attention to the second column. That's Page 114191. That is Hospira 0114191, the**

second column. It's the paragraph that begins with the word overall and concludes with the word neuropathy. Do you see that?

A. **Yes, I do.**

Q. **By the way, before we comment on the substance of that, who is one of the authors on this letter to the editor?**

A. **One of the authors for their letter to the editor is Dr. Alex Sparreboom.**

Q. **Just so we are clear, his name has come up a lot, is this the same Alex Sparreboom that I referred to in opening as the consultant to Hospira?**

A. **Yes, it is.**

Q. **Do you know of any other Alex Sparreboom or men who go by the name of Alex Sparreboom in the oncology business?**

A. **I do not.**

Q. **Will you tell us what Dr. Sparreboom and others report here -- before I go there, is this in the nature of a review article where they are talking about what is in other articles and summarizes it?**

A. **Yes.**

Q. **Now, will you tell us what Dr. Sparreboom and others are reporting there?**

A. **So the authors in the letter to the editor state that the results from their trials, in the trials that were**

commented on in the various publications, published and presented, that the relative systemic exposure to Tween 80 is much lower than with the Cremophor EL. That humans are exposed to lower systemic concentrations of Tween 80 than Cremophor EL and that is as a result of the different rates of elimination from the body. It's consistent with studies reporting that the use of the Cremophor as a formulation vehicle is more likely to result in drug interactions, and also more likely to result in excipient-related toxic side effects. And those side effects include hypersensitivity reactions and neuropathy.

Q. **Is this consistent with studies which say the reported use of Cremophor is more likely than what to result in drug interactions and also more likely to result in excipient-related toxic side effects?**

A. **Cremaphor is more likely than Tween 80 or polysorbate 80.**

Q. **Is Dr. Sparreboom merely comparing Cremophor with polysorbate 80?**

A. **Yes, he is.**

Q. **What is he saying is less likely with polysorbate 80 or, to use an American word, what is he saying is better about polysorbate 80 than Cremophor?**

A. **He is saying that the polysorbate 80 clears from the body much more quickly, so you have less systemic or overall**

exposure.

Q. **Now, let me ask you to turn in your binder to Plaintiffs' Exhibit 208. Have you seen this article before?**

A. **Yes, I have.**

Q. **What is the title of it?**

A. **Rapid Esterase-sensitive Breakdown of Polysorbate 80 and its Impact on the Plasma Pharmacokinetics of Docetaxel and Metabolites in Mice.**

Q. **Do you recognize any of the authors?**

A. **Yes, I do.**

Q. **All of them or just some of them?**

A. **All of them.**

Q. **Does Alex Sparreboom appear again?**

A. **Yes, Dr. Sparreboom is the senior author on this publication.**

Q. **How do you know he is the senior?**

A. **He is the last author for the position reserved for the person who is senior on a publication such as this.**

Q. **I note a lot of these medical articles have multiple authors. Is there any customary practice or traditional practice that you can enlighten us on as to what the order of the names mean?**

A. **In general, for clinical trials, for example, in the Taxol Phase I trial, someone younger like myself at that time, who was the principal investigator doing a lot of the**

heavy work, would be the first author and given that opportunity. And the senior author would be their mentor, the person supervising that work, possibly overseeing the institute or the trials.

In the laboratory the same thing. I would expect Dr. Van Tellingen in this article was probably a person that conducted a lot of the hands-on experiments under the guidance and leadership of Dr. Sparreboom at his institute.

He was the lead person at the Netherlands Cancer Institute in the Netherlands.

Q. Let me ask you to direct your attention to the sentence that begins at the very bottom of Page 300, Hospira 31636 and continues through the paragraph on the next page, Hospira 31636. Go ahead through to the end of the paragraph, Dave, please.

THE COURT: Do me a favor, Mr. Pappas. Please refer to Dave by surname.

MR. PAPPAS: Absolutely, Your Honor.

BY MR. PAPPAS:

Q. Can you tell us what is being reported there by the authors?

A. What they are reporting is that polysorbate 80 is rapidly broken down by plasma and by esterases. So it's unable to exert similar effects as the Cremophor does on the

pharmacokinetics of the taxane. So the polysorbate 80 is eliminated more quickly and thus it doesn't have the same level of interaction on the taxane that the Cremophor does in these mouse models.

Then it states that in patients, the interactions by the polysorbate 80 are even less likely. This is largely due to the fact that the patients are receiving the docetaxel by a one-hour I.V. infusion instead of a bolus injection. The plasma levels remain much lower, so a lower peek concentration and the more rapid breakdown of the polysorbate 80 makes the compound a more favorable component for the formulation/solubilization of water-soluble agents than Cremophor.

Q. **Is this a comparison between polysorbate 80 and Cremophor?**

A. **Yes. They are making a direct comparison between polysorbate 80 and Cremophor.**

Q. **What is the date on this article?**

A. **The date on this article is October 1999.**

Q. **Now, I want to direct your attention now to the drug that we know as Taxotere. Do you have an opinion as to whether the avoidance of anaphylactic shock with Taxotere plays any role in the physician's decision to prescribe?**

A. **Yes.**

Q. **How so?**

A. **You know, the incidence of anaphylaxis, of having a life-threatening toxicity, having a situation where you would occasionally have to have life-saving intervention, certainly in a setting where the drugs have similar FDA indications, where it's permissible to use in the treatment of a patient, doctors will often choose Taxotere as being the preferred product.**

Q. **Now, with respect to the unexpected benefits that you have testified to, do you have an opinion as to whether or not they play any role in the prescription of Taxotere with patients?**

A. **Yes. Just to highlight a few, certainly, the drug-drug interaction component, so commonly utilized in the treatment of breast cancer, are taxanes and anthracyclines. The taxanes, Taxol, Taxotere.**

We have discussed Taxotere. The anthracyclines are drugs that you hear of known as doxorubicin or epirubicin. Those drugs are the two most effective classes of drugs in the treatment of breast cancer.

The initial data with Taxol and doxorubicin was very exciting and there was promising antitumor activity but there was also substantial cardiac toxicity that resulted in the inability of giving those two drugs together. Some schedules were done to separate the drugs in terms of their delivery to avoid those side effects. And that was found to

be due to the drug-drug interaction, altering the pharmacology of the two drugs.

Those results were performed with Taxotere in combination with doxorubicin. Those results were not found. And actually one of the more successful adjuvant breast cancer regimens, the use of TAC chemotherapy, Taxotere with adriomiacin or doxorubicin has been shown to be successful improving the results in women with breast cancer, actually curing women postoperatively with advanced breast cancer.

Q. **I want to turn to the industry generally, the medical profession.**

Has Taxotere received praise as an advance in oncology?

A. **Yes, it does.**

Q. **Let me ask you to turn your attention to Plaintiffs' Trial Exhibit 387. First of all, have you seen it before?**

A. **Yes, I have.**

Q. **What is the title of this article?**

A. **The title of this article is a Phase II Study of Docetaxel in Patients with Paclitaxel-resistant Metastatic Breast Cancer.**

Q. **In what journal did it appear?**

A. **This was published in the Journal of Clinical Oncology.**

Q. **When?**

A. **In October of 1998.**

Q. **Do you recognize any of the authors there?**

A. **Yes, I recognize all of the authors there.**

Q. **Now let me ask you to direct your attention to the first full paragraph on Page SA1003927. It goes over about to the second column.**

Mr. Brooks, could you bring that up, please, and highlight it starting with the docetaxel and paclitaxel and going down to the second column, about midway down, through the word paclitaxel, Footnote 13.

What is being reported there, Dr. Burris?

A. **Here is being reported a discussion comparing docetaxel and paclitaxel both being cytotoxic agents that have a particular mechanism of action promoting tubulin polymerization and a more potent inhibitor of microtubule depolymerization. Although their mechanism of action is similar, the preclinical and clinical activity profiles were noted to be different. Docetaxel is a more potent promoter of tubulin polymerization, a more potent inhibitor of microtubule depolymerization than the paclitaxel. Docetaxel had a greater affinity for the microtubule binding cited. The intercellular biological activity of the taxanes related to their concentration and duration of their exposure, especially in Taxane-resistant cell lines. The cellular uptake of docetaxel is greater than that of paclitaxel and**

its reflux rate is three times slower. These differences may result in higher intracellular concentrations and longer exposure to docetaxel, which may among other differences lead to greater cytotoxic activity. In many in vitro murine and human preclinical modules, including chemotherapy-resistant cell lines, docetaxel has demonstrated greater antitumor activity than paclitaxel in exitoxic doses. The docetaxel is capable of inducing phosphorylation and apoptotic cell death at 100-fold lower concentrations than paclitaxel.

Q. **Let me ask you now to look at the bottom of Page 1003932, the last paragraph in this article that starts with the words In summary and Conclusion at the very top of Page 1003933.**

Mr. Brooks, can you highlight that?

A. **So stated here in the conclusions --**

Q. **Doctor, can we just be clear on something? The reference in these articles is to paclitaxel and docetaxel. Are they referring to just the molecule or the whole product, Taxol and Taxotere?**

A. **Referring to the whole product.**

Q. **When you see paclitaxel, the author is writing about Taxol?**

A. **Yes.**

Q. **When you see the word docetaxel in this article, he is**

writing about Taxotere. Correct?

A. **Yes.**

Q. **So go ahead. What is being reported in that last paragraph?**

A. **In sum, the results of this multi-centered trial show that docetaxel is active in patients with paclitaxel-resistant breast cancer. So active in those patients whose breast cancer has already been treated with Taxol and progressed, worsened. The response rates observed were comparable or superior to those seen with other salvage therapy, to comparable or better than other drugs utilized in this setting. Adverse events were similar to those seen in previous docetaxel studies. So there was no evidence for cumulative toxic effects. So we didn't see additive toxicities by giving the two taxanes in sequence. Although the results of the trial demonstrated the absence of complete cross-resistance to docetaxel in paclitaxel-resistant breast cancer, they do not imply the absence of cross-resistance in patients who may have been treated with paclitaxel for other neoplastic diseases.**

Q. **With all that scientific terminology, can you tell us whether or not this article and the parts you read, does that amount to praise or no praise for Taxotere?**

A. **This amounts to praise. It comments on the fact that not only is Taxotere active in breast cancer, it is actually**

active in breast cancer patients and breast cancer tumors that have not responded to Taxol.

Q. **I want to turn now to opinions you have on infringement of the '561 patent.**

First of all, let me ask you to turn in your book to Joint Trial Exhibit 3.

Is that the '561 patent?

A. **Yes, it is.**

Q. **Have you reviewed it before coming here today?**

A. **Yes, I have.**

Q. **And are you prepared to offer opinions on whether the Hospira and Apotex products infringe Claim 5 of this patent?**

A. **Yes, I am.**

Q. **Now, before we get to the claims specifically, can you turn to the claims that are basically shown in 1, Column 3 and Column 4 specifically, Claim 5, Column 4. Do you have that, sir?**

A. **Yes, I do.**

Q. **There is a reference there to the phrase "being injected without anaphylactic," and we will come to alcohol in a minute, "manifestations being associated therewith"?**

Do you see that?

A. **Yes.**

Q. **I don't want to replow old ground. I think you answered Judge Sleet's question before lunch that**

anaphylaxis manifestations and anaphylaxis are synonyms. Correct?

A. **Correct.**

Q. **Is there additional support for your opinion that we are talking about anaphylaxis in the actual body of the patent?**

A. **Yes, there is.**

Q. **Let me ask you to turn to Column 2 of the patent, Lines 25 through 30.**

MR. PAPPAS: Mr. Brooks, could you bring that up, please.

BY MR. PAPPAS:

Q. **Now, what's reported there, or what's stated there in the patent?**

A. **It's stated that when an injectable solution containing ethanol and a polysorbate 80 surfactant in place of the Cremophor was used in the clinical situation, it became apparent that the anaphylactic reactions were greatly reduced compared with the use of the same solution prepared with Cremophor.**

Q. **What is the reference to the solution with Cremophor?**

A. **Taxol.**

Q. **And that's clear from the patent they are talking about the prior product?**

A. **Yes.**

Q. **And, again, I don't want to repeat testimony we have gone through earlier, but what was the problem with Taxol and anaphylactic reactions?**

A. **The problem with Taxol and anaphylactic reactions was that they were of a severe nature, anaphylaxis, life-threatening, shock-like syndromes, requiring life-saving intervention.**

Q. **May I direct your attention now to the same column, Lines 48 through 51 of the '561 patent. Tell us what is disclosed there?**

A. **So what is stated here is that the anaphylactic shock phenomena which were observed with the solutions of the prior art were not observed with these solutions.**

Q. **What does that mean?**

A. **That the anaphylactic shock phenomena that we see with Taxol are not observed with the Taxotere formulation.**

Q. **Now, are you familiar with the Hospira and Apotex proposed formulations that are the subject of their 505(b)(2) applications?**

A. **Yes, I am.**

Q. **Have you reviewed them?**

A. **Yes, I have.**

Q. **Are there any specific parts of 505(b)(2) applications that you are relying on in forming your infringement opinions on Claim 5?**

A. **Yes, there are.**

Q. **Which ones?**

A. **The labels that are provided as well as the 505(b)(2) applications with the compositions of the products.**

Q. **Do you have an opinion as to whether or not the Hospira proposed formulation contains each and every limitation of Claim 5?**

A. **Yes.**

Q. **What is your opinion?**

A. **My opinion is that it does.**

Q. **Do you have an opinion as to whether the Apotex proposed formulation contains each and every limitation of Claim 5?**

A. **Yes, I do.**

Q. **What is that opinion?**

A. **My opinion is that it does.**

Q. **Now, in conjunction with me and my colleagues, have you prepared a series of demonstrative slides to walk the Court through your infringement analysis and to have it move more expeditiously?**

A. **Yes.**

Q. **Mr. Brooks, can we go to Plaintiffs' Demonstrative Exhibit 2-3.**

What is shown there?

A. **What is shown here, we have the elements of Claim 5 of**

the '561 patent. To the left side I have listed the elements, Elements 1, 2, 3, 4, 5, with the various components that contain that claim.

MR. PAPPAS: Mr. Brooks, can we have the next slide, Plaintiffs' Exhibit 2-4.

Your Honor, I want to cover something here preliminarily, if I might.

I am going to follow this up with the witness.

We understand there is now a debate between the parties about whether or not this is an agreed-upon construction for perfusion. I want to make it clear for the record that at the time Dr. Burris authored his reports, this was the construction agreed upon by the parties.

BY MR. PAPPAS:

Q. **Dr. Burris, is this the construction of perfusion that you used during your reports?**

A. **Yes, it is.**

Q. **And had you been advised by us that this was agreed upon by the parties?**

A. **Yes, I was.**

Q. **Now, for the sake of the rest of my questions, I want you to put aside the agreed construction part of that slide. I ask you, do you have an opinion whether or not that is a correct definition that people in the medical community would understand a perfusion to be?**

A. **Why, that would be an appropriate definition.**

Q. **Particularly, sir, do you have an opinion whether or not that is a proper definition of a perfusion in the context of the '516 and the '512 patents in this case?**

A. **Yes, I do.**

Q. **What is that opinion?**

A. **My opinion is that is the definition. That is the intended use of the term perfusion.**

Q. **Now, there is part of that definition I want to focus on for a minute, where it says, a solution suitable for infusion into patients?**

Does that language have meaning to oncologists?

A. **Yes, it does.**

Q. **What does it mean?**

A. **It means that the product that we are given, that solution, the pharmaceutical agent dissolved into an aqueous solution such as microtubule saline or glucose is intended solely for use in a patient, that it is intended to be given as an intravenous infusion for treating a patient.**

Q. **Are there any well-understood characteristics that such an infusion has in the medical oncological community?**

A. **Yes. So for us to deliver an infusion to a patient, we would take that it solution, that infusion, perfusion, would be safe, that it would be stable, and that it would be reasonably efficacious.**

Q. **Is that safety, efficaciousness and physically stable, is that well understood in the medical oncological community?**

A. **Yes, it is.**

Q. **Let me ask you this: Can you imagine trying to create a perfusion to infuse drugs intravenously into a patient without taking safety, efficacy and stability into account?**

A. **No, I cannot.**

MR. PAPPAS: Now, let's move to the next slide, Mr. Brooks.

BY MR. PAPPAS:

Q. **Can you tell us? You helped in the preparation of these slides. Explain your opinion that Hospira's proposed product is a perfusion.**

A. **This is a proposed box label that Hospira has for the docetaxel injection. Listed on the box is that it's for IV infusion only, that it's for intravenous injection only.**

Q. **And what does that mean that it's IV infusion only?**

A. **That the contents are solely to be given by intravenous infusion. That it is to be given in through a bag attached to a catheter or placed into the vein of a patient for use of a therapeutic.**

Q. **And those words apply to docetaxel injection?**

A. **Yes, they do.**

Q. **As a physician who routinely prescribes Taxotere, and**

they're trying to make the version with docetaxel, is there any other way to get this drug, the one Hospira wants to make, into a human being other than by IV infusion through a bag into the veins?

A. No. The only route is as you described, through intravenous infusion bag device.

MR. PAPPAS: Can we have the next slide, please, Mr. Brooks?

BY MR. PAPPAS:

Q. Does this, the preparation and administration instructions, provide further support for your opinion that the Hospira proposed product is a perfusion?

A. Yes, it does.

Q. Okay. Tell us what parts.

A. The parts, the preparation and administration guideline listed here: the dilution for infusion, particularly number 1, to withdraw the required amount of docetaxel and inject it into an infusion bag of or bottle of either saline or glucose to produce the desired final concentration, is describing what steps should be taken to, in fact, give that docetaxel as an IV infusion.

Q. All right.

A. And then the last sentence, the docetaxel infusion -- excuse me -- the docetaxel injection diluted solution for infusion should be administered intravenously as a 1-hour

infusion under ambient room temperature and lighting conditions.

So, confirming the intent and appropriate administration of the product.

Q. **Is this what Hospira is -- if their instructions were approved, are these directions to the physician?**

A. **Yes, these are the directions for preparation and administration of the product.**

Q. **And what is the purpose of preparations and administration directions with Hospira in a proposed formulation to a physician?**

A. **So the IV is to tell the physicians and their staff how to mix the drugs so they can be given to the patient to treat their cancer.**

Q. **In your opinion, does a pharmaceutical company such as Hospira intend those instructions be followed?**

A. **Yes.**

Q. **Would you follow them?**

A. **Yes.**

Q. **Can you imagine situations where a physician, an oncologist would disregard the instructions from the pharmaceutical company about how to give the medicine?**

A. **No.**

MR. PAPPAS: All right. Can we have the next slide, Mr. Brooks?

BY MR. PAPPAS:

Q. **Now, I want you to go through the basis for your opinion that Apotex's proposed product is a perfusion. Can you tell us what is on the first slide?**

A. **So similarly here, this is the Apotex box label for their docetaxel injection concentrate, with the concentration listed here, and then the top right corner of that, it's intended for intravenous use, intravenous infusion only.**

Q. **Is there any other way to give it? By "give it," is there any other way to give Apotex's product?**

A. **No. These drugs, this drug can only be given through an intravenous bag device, mixed in a bag or bottle, hooked to catheter and delivered into the vein of the patient.**

Q. **In your opinion, is that a perfusion?**

A. **Yes.**

MR. PAPPAS: Can we go to the next slide, Mr. Brooks?

BY MR. PAPPAS:

Q. **Now, what is shown here on Plaintiff's Demonstrative Exhibit 8?**

A. **Similar to the prior description, there are also instructions for mixing, diluting and infusing the drug. Label No. 1 is the technique to withdraw the diluted docetaxel injection and also to put it into an infusion bag**

or bottle of either saline or sugar or dextrose to produce the final concentration.

And then the final sentence, that the final docetaxel injection dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

Q. **Is there any other way, in your opinion, to give the Apotex infusion other than perfusion?**

A. **There is not.**

Q. **In the medical profession, is there a standard custom and practice about whether or not you follow the directions given by a pharmaceutical company for the use of medications?**

A. **Yes. In particular, with an intravenous medication such as those listed here, which will be mixed, prepared in a clinic, the instructions are followed quite rigorously.**

Q. **Why is that?**

A. **For safety precautions and to ensure the correct dose is administered to the patient, and it's administered in the most safe and stable form possible so we can obtain the therapeutic effect that is desired.**

MR. PAPPAS: All right. Let's go to the next slide.

BY MR. PAPPAS:

Q. **What is shown here, sir, as further support for your**

infringement opinion for the Hospira perfusion?

A. **So listed here, I have a pointer. For Elements 2, 3, and 4, the various components that are listed, docetaxel, the ethanol and the polysorbate 80, listed here are the components. And then listed here by my calculations are the Hospira perfusion at maximum concentration.**

In each of these cases, with the docetaxel, meets Element 2, contains approximately 1 milligram per ML of docetaxel, containing .74 milligrams per ML.

Element 3, that it contains less than 35 milliliters per liter of ethanol, and the ethanol is 17.0 milliliters per liter.

And Element 4, it contains less than 35 milliliters per liter of polysorbate 80, and it contains 17.9 milliliters per liter of polysorbate 80.

MR. PAPPAS: All right. Mr. Brooks, can we have Plaintiff's Demonstrative Exhibit 2-10?

BY MR. PAPPAS:

Q. **Can you please give us how you support your opinion that Apotex's proposed product met Elements 2-4?**

A. **So, similarly, highlighted Elements 2, 3, and 4, in the table that is associated, the same math applies, provided in the Apotex (b)(2) application. Element 2, the docetaxel, is less than 1 milligram per ML, at .47 milligrams per ML. The ethanol is less than 35**

milliliters per liter. It's actually 4.55 milliliters per liter. And the polysorbate 80, less than 35. It's actually 17.8 milliliters per liter.

Q. **All right. Thank you.**

MR. PAPPAS: Mr. Brooks, can we have Plaintiffs Demonstrative Exhibit 2-11.

BY MR. PAPPAS:

Q. **Now, will you explain how this slide supports your opinion that Hospira's perfusion meets the limitation of the fifth element of Claim 5?**

A. **Yes. Element 5 is construed as having a reasonable expectation of being injected without causing anaphylactic or alcohol intoxication manifestations.**

The Hospira label in fact states, it is listed here, severe hypersensitivity reactions characterized by generalized rash, erythema, hypertension and/or bronchospasm or, very rarely, fatal anaphylaxis in patients.

MR. PAPPAS: Can we have the next slide, Plaintiff's Demonstrative Exhibit 2-12.

BY MR. PAPPAS:

Q. **This refers to the Apotex perfusion. And what is contained there that supports your opinion that the Apotex perfusion meets the fifth element of Claim No. 5?**

A. **That, Claim No. 5, Element No. 5, having the same statement, to a reasonable expectation of being injected**

without causing anaphylactic or alcohol intoxication manifestations. And the label stated severe hypersensitivity, including very rare fatal anaphylaxis, has been reported in patients.

Q. **Now, going back to Hospira. Does Hospira and Apotex rely on the Taxotere label in their 505(b)(2)?**

A. **Yes, they do.**

Q. **Doctor, does the reporting in the labels of Apotex and Hospira that come from Taxotere as well as vere rare anaphylaxis, does that comport with your clinical practice?**

A. **Yes.**

Q. **Now, I asked you about death before. And you said you had it with two patients on Taxol; correct?**

A. **Correct.**

Q. **Have you ever lost a patient due to anaphylaxis that was on Taxotere?**

A. **I have not.**

Q. **Have you had any cases of anaphylaxis with Taxotere that you were able to recover?**

A. **I have not.**

Q. **Have you ever had a patient on Taxotere have anaphylaxis while they were getting the drug?**

A. **I have not.**

Q. **And how many patients over your career have you treated or administered on Taxotere?**

A. **Administered or supervised more than 1,000 patients receiving Taxotere.**

Q. **And did any of these receive premedication of corticosteroids and antihistamines likes Taxol?**

A. **No.**

MR. PAPPAS: Okay. We can go to the next, Plaintiff's Demonstrative Exhibit 2-13.

THE COURT: Mr. Pappas, let's take a too-much-coffee break. Okay?

MR. PAPPAS: Absolutely, Your Honor. I understand.

(Brief recess taken.)

THE COURT: All right. Please be seated. Let's continue.

MR. PAPPAS: May I proceed, Your Honor?

THE COURT: Yes.

MR. PAPPAS: Thank you.

Mr. Brooks, can I have Plaintiff's Demonstrative Exhibit 2-11?

BY MR. PAPPAS:

Q. **Dr. Burris, I have a couple questions here I may not have asked you.**

In the proposed labeling of Hospira's perfusion where they refer to very rarely fatal anaphylaxis, do you see that?

A. **Yes, I do.**

Q. **Now, based on your review of the proposed labeling of Hospira's product, is it copied from the label for Taxotere?**

A. **Yes, it is.**

Q. **Now, do you know if the Taxotere label that reports very rare fatal anaphylaxis, is that based on the Integrated Safety Summary results that we have already gone through?**

A. **Yes, it is.**

Q. **And I think -- and what did the Integrated Safety Summary results indicate as the maximum amount of anaphylaxis?**

A. **So the Integrated Safety Summary for all the patients from the trials, they listed Grade 4 for anaphylaxis as 0.6 percent.**

Q. **All right. So, now, I have a question for you. Do you have an opinion as an oncologist, as a physician, if you read the Hospira label and the Apotex proposed labels that have very rarely fatal anaphylaxis, and you know it's based on the Taxotere label that is based on the Integrated Safety Summary, do you have any conclusion about what that would tell you as a physician as to the likely incidence of anaphylaxis?**

A. **That it would be extremely low.**

Q. **Less than what percent?**

A. **Certainly less than two percent, probably less than**

one percent.

Q. Very well.

MR. PAPPAS: Let me ask you, Mr. Brooks, to bring up Plaintiff's Demonstrative Exhibit 2-13.

BY MR. PAPPAS:

Q. Now we're on the last element of Claim 5. Can you explain how this slide assists you in explaining your opinion that the defendants' perfusion, both Apotex and Hospira, can be administered without having a reasonable expectation of alcohol intoxication?

A. Yes. So as Element 5 has stated, having a reasonable expectation of being objective, without causing anaphylactic or alcohol manifestations, the alcohol levels that are administered using Hospira and Apotex proposed products amounts to less than a third of a standard serving of alcohol.

And that concentration and the math below I worked out utilizing the specific gravity of alcohol, looking at a standard dose of Taxotere that would be delivered and looking at the total amount that would be administered, and, in both cases, far less than what would be given, for example, on a standard 12-ounce beer or a small glass of wine; in fact, less than four ounces of, four milliliters of alcohol. Less than a third of a drink.

MR. PAPPAS: Mr. Brooks, may I have the next

slide? Plaintiff's Demonstrative Exhibit 12-14.

MR. ALY: Objection to the exhibit. It's outside the scope of the report. This is one of the ones we had talked about earlier with counsel and we discussed when it came up.

MR. PAPPAS: Your Honor, if I may.

Dr. Kibbe is one of the Apotex witnesses. And on Page 21 of the Kibbe responsive report, he opined that he used the AMA medical standard where he said if this were administered in a single bolus injection, the levels would be estimated --

MR. ALY: Your Honor, would you like to -- can we have a sidebar on this issue? I'm sorry to interrupt.

THE COURT: We can take it to sidebar.

MR. PAPPAS: Sure.

(Conference held at sidebar out of presence of witness.)

THE COURT: Okay. Your objection.

MR. ALY: Yes, Your Honor. I interrupted Mr. Pappas. He was reading from Mr. Kibbe's report. That's why I objected, because he was reading from a third-party report.

THE COURT: Okay. That's fine.

MR. PAPPAS: Your Honor, Dr. Kibbe submitted several reports, but in his responsive report of July 24,

2009, he specifically referred to the AMA standards for alcohol that had been once .08 and fallen as low as .04 grams per 100 milliliters. And with that as a foundation, he concluded, Dr. Kibbe, that is, in his report, that even using -- he wasn't specifically calling out AMA but he said that in his conclusion, he said, therefore, Apotex's product --

THE COURT: Hold on. April, come on. This is a United States courtroom.

THE DEPUTY CLERK: Counsel.

THE COURT: (Addressing the courtroom.) Counsel, if you want to have a conversation, take it outside.

MR. PAPPAS: Sorry. Thank you.

He concluded that the Apotex formulation could be administered without fear of anaphylaxis or alcohol intoxication manifestations being associated therewith.

And in Dr. Burris's report, it then responded to that he, Dr. Burris, agreed that the product could be administered without alcohol intoxication. And Dr. Burris understood that he was responding to the entire Kibbe report, including the references to the AMA standard.

Now, all that is on this slide, Your Honor, is that it is another way of demonstrating that the Hospira perfusion, Apotex perfusion contains less alcohol than even

the AMA standard of .04. It's a simple mathematical calculation.

Both counsel are certainly free to cross-examine, but I don't think there is any surprise here. And I think this testimony is, can be of assistance to the Court because the bottom line is this: When you measure the alcohol content, the ethanol content of the perfusions of Apotex and Hospira, whether you measure it by a standard drink of alcohol or whether you measure it by the AMA standard for intoxication or being impaired, .04 or .08 percent, the fact is these defendants' perfusions have less alcohol than that. That is all we're attempting to establish.

I don't think there is any unfair surprise. In fact, Dr. Kibbe, Apotex's expert, is the one that first referred to the AMA standard.

THE COURT: Counsel.

MR. ALY: Your Honor, Dr. Burris is the one testifying to the standard, not Dr. Kibbe. In his Rule 26, the AMA approach was never offered by Dr. Burris, in his opening rebuttal or even responsive report. What I hear Mr. Pappas to say is that Dr. Burris agreed.

THE COURT: Speak up a little bit.

MR. ALY: What I hear Mr. Pappas to say is he agreed with Dr. Burris and Dr. Kibbe. They both agreed on

the conclusion whether you can avoid alcohol intoxication manifestations. If he can do that in another way, another analysis, that's fine if they want to do that, but not to use the AMA with Dr. Burris. And since it's infringement, it should have been in the first report, but it wasn't stated until the third report. They're adding by inference, since they agreed on the conclusions, they can agree what Dr. Kibbe said in the record.

THE COURT: Fair enough. If what counsel has said is accurate, in terms of the reports, I don't see how this gentleman can opine in that way if they have not been put on notice, in all fairness, Mr. Pappas.

MR. PAPPAS: Your Honor, if I may. They put it in issue.

THE COURT: They may have put it in issue, but your expert hasn't offered it as an basis for any of his opinion in the 26 report. That is what is being asserted here.

MR. PAPPAS: Excuse me, Your Honor.

THE COURT: It's a question of notice, and you say they're not prejudiced or unfairly surprised. He says exactly the opposite. He has not had a chance to depose this gentleman on this particular point insofar as this particular expert's opinion upon whom he is relying, and it doesn't seem to be a point of great controversy and easily

established by you in another way.

I'm going to grant the objection. We're going to move on.

MR. PAPPAS: Very well, Your Honor.

(Conference at sidebar ends. Proceedings continue in open court.)

THE COURT: It's a United States Court, ladies and gentlemen. Please act appropriately.

You may proceed.

MR. PAPPAS: Your Honor, I understand you have sustained the objection to Plaintiffs' Demonstrative Exhibit 214?

THE COURT: That would be correct, yes.

BY MR. PAPPAS:

Q. Let me go back to Demonstrative Exhibit Plaintiffs' 2-13.

That is your opinion that you just testified that both of the perfusions of Hospira and Apotex have less than one-third of the standard serving of alcohol in their perfusions. Is that correct?

A. Yes, it is.

Q. Are you aware of any measure whatsoever or any understanding of alcohol intoxication by which the amount of alcohol in Hospira-Apotex perfusions would exceed? Is there any standard you are aware of?

A. **No.**

Q. **Again, is the labeling of the proposed Hospira and Apotex perfusions virtually identical to the Taxotere label?**

A. **Yes, they are.**

Q. **And you have testified today about how much Taxotere you have administered?**

MR. ALY: Your Honor, these are leading questions.

THE COURT: Sustained.

BY MR. PAPPAS:

Q. **Do you have an opinion as to whether or not Taxotere is administered daily with a reasonable expectation of avoiding alcohol intoxication manifestations?**

A. **Yes, I do.**

Q. **What is that opinion?**

A. **My opinion that it isn't unreasonable that you can expect to inject it without alcohol intoxication.**

MR. PAPPAS: Might I have a moment, Your Honor?

THE COURT: Yes, sir.

(Pause.)

MR. PAPPAS: I think that is all the questions I have for Mr. Burris at this time. Thank you.

THE COURT: Counsel, you may cross-examine.

MR. ALY: Thank you, Your Honor.

May it please the Court...

THE COURT: Sure.

CROSS-EXAMINATION

BY MR. ALY:

Q. **Dr. Burris, it is good to see you again.**

A. **Thank you, sir.**

Q. **How are you?**

A. **I am fine. Thank you.**

Q. **I want to clarify, you are a medical doctor. Right?**

A. **Yes.**

Q. **You are not a formulator?**

A. **I am not.**

Q. **You put up an article by Dr. Weiss and talked about that one in your direct examination?**

A. **Yes, I did.**

Q. **You know Dr. Weiss, don't you?**

A. **Yes.**

Q. **Dr. Weiss is a medical doctor. Right?**

A. **Yes.**

Q. **He is not a formulator?**

A. **Correct.**

Q. **You worked with Dr. Von Hoff, you trained with him. Right?**

A. **Yes.**

Q. **And Dr. Van Hoff is a medical doctor. Right?**

A. **Correct.**

Q. **Dr. Van Hoff is not a formulator. Correct?**

A. **Yes.**

Q. **You put up an article by Alex Sparreboom, Van Zuylen, you saw that. Right?**

A. **Yes.**

Q. **Have you ever met Dr. Sparreboom?**

A. **I have seen Dr. Sparreboom lecture. I am not sure whether I have met Alex or not. I know his colleague Jacques Fabre very well.**

Q. **You know Dr. Sparreboom is not a formulator. Is that true?**

A. **I don't know that. Dr. Sparreboom is --**

Q. **Do you know whether Dr. Sparreboom is a formulator?**

MR. ALY: Your Honor...

THE WITNESS: I do not.

MR. PAPPAS: Objection, Your Honor. Can he finish his answer?

BY MR. IMRON:

Q. **When you were in medical school, that was in the mid-eighties. Is that right?**

A. **Yes.**

Q. **And you had conversations with Dr. Von Hoff, your mentor, about Taxol?**

A. **Yes.**

Q. **The drug in Taxol is called paclitaxel. Correct?**

A. **Correct.**
Q. **And the drug in Taxotere you have been talking about today, that is called docetaxel. Right?**
A. **Correct.**
Q. **Those two may be related but they are different drugs, aren't they?**
A. **Yes, they are.**
Q. **They have different strengths, don't they, potencies, if you will?**
A. **Yes.**
Q. **They have different solubilities, in other words, how much they mix into different solutions, that is different between the two. Right?**
A. **I am not an expert on that. I don't know the answer to that.**
Q. **You haven't considered whether or not there are differences between paclitaxel, the thing used in Taxol, and docetaxel, the thing used in Taxotere, to see if they might dissolve differently in liquids. Right?**
A. **Correct.**
Q. **You have not looked at that issue at all. Isn't that true?**
A. **I personally have not. I have read the literature on it, spoken with people and participated in discussions and research on those issues.**

Q. **Now, on the research that you have done, that was to look at docetaxel as used in Taxotere. Isn't that true?**

A. **Yes.**

Q. **And that's in clinical practice, you have administered Taxotere and monitored what was happening to patients with that drug. Correct?**

A. **Correct.**

Q. **Taxotere happens to have docetaxel in a formulation of polysorbate 80, doesn't it?**

A. **Yes.**

Q. **But if somebody in the United States wanted to get docetaxel, that drug, the only formulation they have to get it in is Taxotere. Right?**

A. **Correct.**

Q. **That means if somebody wants docetaxel, that drug, that active ingredient, the only formulation choice they have is polysorbate 80. Right?**

A. **Correct.**

Q. **In fact, it's never been clinically compared, the same active ingredient, either docetaxel or paclitaxel, in both a Cremophor formulation and a polysorbate 80 formulation. Isn't that true?**

A. **I don't know that to be true.**

Q. **Do you know of any clinical trial that compares the same active ingredient in polysorbate 80 on the one side and**

Cremophor on the other side?

A. **If you can clarify. I am aware of clinical trials that have compared docetaxel and polysorbate 80 with paclitaxel or Taxol in Cremophor.**

Q. **I understand that. That is a little bit different to my question, which is: Do you know of any clinical trials which have the same drug, pick whichever one you want, docetaxel or paclitaxel, but tested in two formulations, one with polysorbate 80 and one with Cremophor?**

A. **I am aware of clinical trials of paclitaxel being tested in Cremophor and paclitaxel being tested in other formulations. And I don't know the level of components of those polyglutamated formulations, Vitamin E emulsions. There have been a number of formulations of paclitaxel that have been tested other than Cremophor clinically.**

Q. **I am asking about two of them, Dr. Burris.**

A. **Okay.**

Q. **A formulation of docetaxel, let's start there, in Cremophor, has that ever been tested clinically?**

A. **I don't know of docetaxel being tested in clinical trials.**

Q. **A form of paclitaxel in polysorbate 80, has that ever been tested clinically?**

A. **Not that I am aware of in a pure polysorbate 80 formulation.**

Q. **Now, if one drug is more soluble than another drug, could dissolve easier, wouldn't you agree that you wouldn't need as much excipient with that drug?**

THE COURT: Would you say that again? I am sorry.

BY MR. ALY:

Q. **Sure. An excipient is the ingredients that go with the active ingredient. You understand that. Right?**

A. **Yes.**

Q. **So if it's a formulation and there is some active ingredient, and there is some excipients that go with that. Correct?**

A. **Correct.**

Q. **And if one drug is more soluble, it dissolves easier, you don't need as much of the excipients that go with it. Correct?**

A. **I am hesitant to answer and feel like I might be outside the scope of my expertise in the sense that from the lectures I have heard and the material I have read on formulation, there is a number of reasons for the amount of excipient that is utilized, stability and the like.**

So I don't know that I can answer that.

Q. **I am asking about one of them, Dr. Burris. If one drug is more soluble than another drug, wouldn't you agree that you would need as much excipients with the more soluble**

drug?
A. I don't know that to be true.
Q. We had a deposition in this case, didn't we?
A. Yes, sir, we did.
Q. I asked questions and you answered. Correct?
A. Yes.
Q. And you were under oath in that deposition. Correct?
A. Yes.
Q. I asked this question and you answered this way. The question in the deposition is starting at Page 131, Line 50:
"Question: For example, if one drug is more soluble than another drug, wouldn't you agree that if the drug is more soluble, then you would not need as much excipients with that drug?
"Answer: Yes."
Did you give that answer to my question, sir?
A. Yes.
Q. If a drug is more potent over the course of delivery, you also wouldn't need as much excipients to go with it. Right?
A. I honestly don't know. I don't believe that potency would have a direct relationship with the amount of excipient that was needed.
Q. In honesty, you just don't know. Is that what you are saying?

A. **Correct.**

Q. **If you are being honest, you don't know?**

A. **Correct.**

MR. ALY: Could you please play the video at Line 20.

"Question: And if the drug is more potent over the course of the delivery of that drug, you would not need as much excipients either. Correct?

"Answer: That's correct."

BY MR. ALY:

Q. **Did I ask you that question and did you give me that answer in the deposition?**

A. **Yes.**

MR. PAPPAS: Your Honor, I don't think that is an appropriate objection. He gives the same answer.

THE COURT: I am going to sustain that objection and strike that response.

I think it's the same question. It wasn't impeaching, as I understood it.

You can start again if you think you have gotten an answer that you are not happy with.

BY MR. ALY:

Q. **Docetaxel, that drug is more soluble than paclitaxel, isn't it?**

A. **I apologize for the hesitation. It's proven to be**

more soluble. The taxanes were very difficult to solubilize. Taxotere's formulation has been utilized in polysorbate 80 --

THE COURT: Doctor, let me get you to just respond to his question.

Why don't you restate the question.

MR. ALY: Yes, Your Honor.

BY MR. ALY:

Q. **Docetaxel is more soluble than paclitaxel as a compound, isn't it, sir?**

THE COURT: Answer if you can. If you can't --

THE WITNESS: I don't know that to be for certain true.

THE COURT: Do you think you have something?

MR. ALY: Yes, Your Honor.

THE COURT: Go right ahead.

MR. ALY: Could you please go to Page 140, Line 2:

"Question: And docetaxel is more potent than paclitaxel as a compound. Correct?

"Answer: Correct."

BY MR. ALY:

Q. **Did I ask you that question and you gave that answer at the deposition, sir?**

A. **Yes, but that's a different --**

Q. **I just asked you if you answered it that way.**

THE COURT: You will get a chance to have your counsel redirect you on that point.

MR. PAPPAS: Your Honor, if I may, I recall before lunch in the direct I attempted or asked a series of questions which Mr. Aly thought were in the area of formulation, pure formulation. And he objected. As I recall, Your Honor -- but your memory will control here -- you said, he is not a formulator; reformat your question. And I then directed all the rest of my questions --

THE COURT: You did. That is why you will get a chance to redirect him in those areas.

MR. PAPPAS: Thank you, Your Honor.

BY MR. ALY:

Q. **Would a formulator know more than a medical doctor would about formulation issues, Dr. Burris?**

A. **Yes.**

THE COURT: I should say he did. And that is why you are going to get a chance to redirect.

MR. PAPPAS: I understand, Your Honor.

BY MR. ALY:

Q. **Let's look at one of the medical papers that you put up, PTX-553, please. This is one with of the papers that you have relied on in the direct examination. Right?**

A. **Yes, it is.**

Q. **That is by a Dr. Kris?**

A. **Yes, it is.**

Q. **That was in 1986; is that correct?**

A. **Correct.**

Q. **Let's go to the third page of this exhibit, please, the last paragraph?**

The Kris paper is describing hypersensitivity reactions. Correct?

A. **Correct.**

Q. **Those reactions are severe and unpredictable treatment-limiting toxicity. Correct?**

A. **Correct.**

Q. **Now, Dr. Kris isn't talking about anaphylaxis, is he, he is talking about hypersensitivity. Right? Isn't that what it says right there, Dr. Burris?**

THE COURT: That's two different questions, counsel. You asked what he is talking about and whether it's what it says there. Which one do you want him to answer?

BY MR. ALY:

Q. **The question I would like to ask is doesn't the paper report that hypersensitivity reactions constitute a severe toxicity, Dr. Burris?**

A. **Yes.**

Q. **Doesn't the paper report that further studies are**

needed to determine what to do about those hypersensitivity studies, reports?

A. **Yes.**

Q. **There are a few options of what could be done in the mid-eighties, isn't that true, to address hypersensitivity reactions with Taxol?**

A. **Correct.**

Q. **One of those actions is pretreatment regimens. Isn't that true?**

A. **Yes.**

Q. **That would include steroids, for example, wouldn't it?**

A. **Yes.**

Q. **Another option is alternative schedules, isn't that another option?**

A. **Yes.**

Q. **That means making it longer, a few hours longer to administer. Correct?**

A. **Correct.**

Q. **Another way of altering the schedule instead of every week, you would have it every three weeks. Correct?**

A. **Correct.**

Q. **The third option describing the Kris paper is a reformulated preparation. Is that true?**

A. **Yes.**

Q. **And you have had experience in Phase I clinical**

trials, haven't you?

A. **Yes.**

Q. **You know it takes years to go through those, don't you?**

A. **Years to complete those trials?**

Q. **Yes.**

A. **Yes.**

Q. **If somebody wanted to look at this paper that you found and simply use pretreatment instead of the other options, they could do that, couldn't they?**

A. **Yes.**

Q. **In fact, with Taxol they started using -- after they saw a problem with hypersensitivity reactions, they started using premedication, didn't they?**

A. **Yes.**

Q. **And to this day Taxol is available on the market with premedication, isn't it?**

A. **Yes.**

Q. **Sometimes you prescribe Taxol to people, don't you?**

A. **Yes.**

Q. **Dr. Burris, I would like to call up your slide, PDX-2-2.**

This was your slide listing some of the unexpected benefits with Taxotere formulation. Correct?

A. **Correct.**

Q. **We have talked about how Taxotere has two differences to Taxol, doesn't it?**

A. **Does Taxotere have two differences with Taxol?**

Q. **Let me be clear in my questioning. In the formulation of differences between Taxol and Taxotere, they have different active ingredients. Right?**

A. **Correct.**

Q. **In the formulation of Taxol and Taxotere, they have different surfactants. Right?**

A. **Correct.**

Q. **One uses Cremophor as a surfactant, that's the Taxol, the other uses polysorbate 80 as a surfactant, that's the Taxotere. Right?**

A. **Correct.**

Q. **Now, at some point there was a comparison made between those two formulations. Is that true?**

A. **I don't understand the question. You mean clinically? Preclinically?**

Q. **Let me ask you this: When the polysorbate 80 clears the bloodstream faster, that was determined preclinically, wasn't it?**

A. **Yes.**

Q. **And that's true in animal studies. Correct?**

A. **Correct.**

Q. **The impact of that on a human, we don't know yet the**

difference between polysorbate 80 and Cremophor. Correct?

A. **I believe we do.**

Q. **Now, the day before the comparison was made, the one you are talking about, was there any expectation about the polysorbate 80 and whether it would clear faster or slower than Cremophor?**

A. **The day before the Van Tillingen article?**

Q. **Let me rephrase the question.**

Dr. Burris, before polysorbate 80 was actually tested, there wasn't any expectation one way or the other about what would happen with it. Right?

A. **Correct.**

Q. **It just had to be tested. Right?**

A. **Correct.**

Q. **And that means the day before the comparison was made, people just didn't know what to expect, and the day after they figured something out. Right?**

A. **Correct.**

Q. **And the same is true for the linear pharmacokinetics. Right?**

A. **The linear pharmacokinetics came from the Phase I trials.**

Q. **So, again, before the formulation with polysorbate 80 was tested, there was no expectation one way or the other about what would happen with linear pharmacokinetics.**

Correct?

A. **Correct.**

Q. **Then after it was tested they found linear pharmacokinetics. Right?**

A. **Yes.**

Q. **It's just something that had to be tested. Right?**

A. **Yes.**

Q. **Clinical side effects, that was also tested to see after a polysorbate 80 formulation was developed what would happen. Right?**

A. **Correct.**

Q. **Before that, were there any expectations about whether polysorbate 80 would reduce side effects or not?**

A. **No.**

Q. **What about drug-to drug interactions? That is something that is also just tested after a formulation is developed. Right?**

A. **Correct.**

Q. **Before polysorbate 80 was used in the Taxotere formulation, was there any expectation about drug-to-drug interactions?**

A. **Not that I am aware of.**

Q. **Just something that had to be tested. Right?**

A. **Correct.**

Q. **Neuropathy, that was something tested after**

polysorbate 80 was used in the Taxotere formulation. Right?

A. **Yes correct.**

Q. **Now, before polysorbate 80 was used in that formulation, was there anything expected one way or the other about what would happen with neuropathy?**

A. **Not that I am aware of.**

Q. **It's just something that had to be tested. Right?**

A. **Correct.**

Q. **A lot of the testimony that you described compared Taxotere to Taxol. Isn't that true?**

A. **Yes.**

Q. **We talked about the fact that they have different active ingredients. Right?**

A. **Yes.**

Q. **We talked about the fact that they have different surfactants in them. Right?**

A. **Yes.**

Q. **In fact, they are also administered differently, aren't they?**

A. **Yes.**

Q. **Taxol is given how frequently?**

A. **Taxol is given on a variety of schedules. The Taxol label is a three-hour infusion once every three weeks.**

Q. **That's not the same way that Taxotere is administered, is it?**

A. **Taxotere is administered as a one-hour infusion every three weeks.**

Q. **So there is a three-hour infusion and there is a one-hour infusion. Right?**

A. **Correct.**

Q. **Taxol has a different dose, the amount that you give to the patient. Correct?**

A. **Yes.**

Q. **Taxol has 175 milligrams per square meter. That's how you calculate that dose. Right?**

A. **Correct.**

Q. **For Taxotere, it's 100 milligrams per square meter. Right?**

A. **Correct.**

Q. **When the dose goes higher, you are giving more of the excipients than other ingredients that go with it. Correct?**

A. **Correct.**

Q. **And so if you are giving Taxol, you have to giver 1.75 more times, one and three-fourths more times of the excipients that go with it for one dose of that drug. Right?**

A. **No.**

Q. **So when there is paclitaxel in Taxol, that is 175 milligrams per square meter. Right?**

A. **Correct.**

Q. **So when you measure out that drug, you give 175 times the drug you give for Taxotere? Isn't that true?**

A. **You give 1.75 times the active ingredient.**

Q. **And so that's just the active ingredient. When you look at the excipients that go with it, it's even a higher percentage, a higher multiple that goes with Taxol than with Taxotere. Right?**

A. **I don't want to answer that incorrectly. I think the comparison you are making, if I could answer, it can only be done drug within drug. So a hundred per meter squared of Taxotere versus 50 per meter squared is twice as much polysorbate 80.**

There is no polysorbate 80 in Taxol. So giving 175 versus a hundred of Taxol is a 1.75 times increase in the amount of Cremophor that is given. I don't think you can compare across those two agents for that.

Q. **You just can't make a comparison between Taxol and Taxotere, can you?**

A. **Correct.**

Q. **If we could please go back to PDX-202.**

These were some of the unexpected benefits again that you listed, you looked at just a moment ago. Right?

A. **Yes.**

Q. **Isn't it possible that the changes between Taxol and Taxotere, it's not the formulation, but the drug that's**

responsible for any of these benefits? Isn't that possible?

A. **Not for the ones listed here.**

Q. **Isn't it possible that the drug itself, docetaxel, might actually contribute to some of the side effects differently than paclitaxel?**

A. **True.**

Q. **So when we are trying to look at -- I will pick side effects. When we are trying to look at that, you have to look at the differences in the drugs themselves, the active ingredients, and not just the formulation, don't you?**

A. **Yes.**

Q. **Now, if we could go to please PDX-2-11.**

I am going to now ask you about the infringement contentions that you have got of Claim 5 against the Hospira product. Is that okay?

A. **Yes.**

Q. **This is your slide about that issue. Right? 2-11?**

A. **Correct.**

Q. **And in that slide you are looking on the left side as one of the elements in Claim 5. Right?**

A. **Yes.**

Q. **As construed, there is a brief construction that that means having a reasonable expectation of being injected without causing anaphylactic or alcohol intoxication manifestations. Right?**

A. **Yes.**
Q. **That's the claimed construction. Correct?**
A. **Correct.**
Q. **For your proof of infringement you are comparing it to this part of Hospira's label. Correct?**
A. **Correct.**
Q. **And the part on Hospira's label that you highlighted says very rarely fatal anaphylaxis, doesn't it?**
A. **Yes.**
Q. **That is anaphylaxis, the narrow word that you took to mean anaphylactic manifestations. Right?**
A. **Correct.**
Q. **Sometimes, sometimes, according to the label, Hospira's product will kill people. Right?**
A. **According to the label.**
Q. **And it's the same label as Taxotere's product. Right?**
A. **Correct.**
Q. **Sometimes, sometimes Taxotere's product kills people, unfortunately. Correct?**
A. **I don't know that that has ever been reported.**
Q. **You have not seen the reports?**
A. **For anaphylaxis --**
Q. **For anaphylaxis?**
A. **With Taxotere I have not seen anaphylaxis-reported death from Taxotere, no.**

Q. **The FDA has required this exact label on the Taxotere product. Correct?**

A. **I know that's the wording on the Taxotere label.**

Q. **So when Taxotere is given to a patient, this label goes with it, that it may cause very fatal -- rarely fatal anaphylaxis. Correct?**

A. **Correct. The label is a warning.**

Q. **And the warning is something that the FDA evaluates to make sure people know what the risks are. Right?**

A. **Correct. But in the integrated safety summary, there is no reported anaphylaxis deaths.**

THE COURT: From Taxotere.

THE WITNESS: From Taxotere. And that's where the label was created are from.

BY MR. ALY:

Q. **Sir, are your saying there was no anaphylaxis deaths or are you saying there was no anaphylaxis?**

A. **There was 0.6 percent Grade 4 allergic reactions, which would be anaphylaxis. And there was no fatal reports from the 12 patients that were listed as dying within that report.**

Q. **Even if we accept the understanding you have got of this term, that anaphylactic manifestations means anaphylaxis, you are not saying it never happens. Right?**

A. **I have never seen it happen. I personally have never**

seen it in the patients I have treated. There is 0.6 percent Grade 4, which is anaphylaxis in the integrated safety summary, which is used to make the label.

Q. **That 0.6 percent that was used, it happens, doesn't it, anaphylaxis happens?**

A. **According to that integrated safety summary, yes.**

Q. **And the integrated safety summary is based on all of the clinical data that Sanofi had available to it as of the time that it was turned into the FDA. Correct?**

A. **Correct.**

Q. **And that has more patients than you personally saw. Correct?**

A. **Yes.**

Q. **And the integrated safety summary, that table that you relied on, that table included information of the overall population, didn't it?**

A. **Correct.**

Q. **Please pull that up, JTX-69, Page 76.**

This is the table that you looked at?

A. **Yes.**

Q. **If you would just highlight the table title. That table 43A is the title for the table that you relied on. Correct?**

A. **Yes.**

Q. **This is where your 0.6 percent number comes from.**

Right?

A. **Correct.**

Q. **If you look at the heading you described on direct what non-hematological toxicity means, didn't you?**

A. **Yes.**

Q. **So in other words, they are varying overall?**

A. **Yes.**

Q. **And overall means there are different categories of people grouped all together for the results show here. Right?**

A. **Yes.**

Q. **This is -- if I can clarify, so this is all patients created a hundred milligrams per meter squared. So these are all those patients are grouped together in this Table 4, isn't that true?**

A. **Yes.**

Q. **That table reports an overall number that groups them all together. Right?**

A. **Yes.**

Q. **When it does that grouping, it includes patients, doesn't it, that received premedication treatment?**

A. **Yes.**

Q. **In fact, there are different groups of people that were actually, in fact, combined to get to this number, weren't there?**

A. **Correct.**
Q. **One of those had what was called Type I premedication?**
A. **Correct.**
Q. **Another one was Type 2 premedication. Correct?**
A. **Correct.**
Q. **Another was Type 3 premedication. Correct?**
A. **Correct.**
Q. **Some patients also had no premedication. Correct?**
A. **Correct.**
Q. **This is a unique point that I learned about, there is a fifth group called Other within this category system. Right?**
A. **Yes.**
Q. **And that means that they didn't start off with premedication, but while taking Taxotere they needed the premedication. Correct?**
A. **Or that the physician administered it, yes.**
Q. **Either way, the physician administered steroid premedication at some point during the treatment cycles for that category of patients called Other. Right?**
A. **Correct.**
Q. **And so when we were looking at the data that is shown here in Table 43A, that is really including all those people including those ones that were pretreated with steroid and then getting to that 0.6 number; correct?**

A. **Right.**
Q. **Premedication wasn't required at first with Taxotere; is that correct?**
A. **Correct.**
Q. **But over time, hypersensitivity reactions occurred, didn't they, with Taxotere?**
A. **Are those questions linked? There was no premedication instituted for hypersensitivity reactions.**
Q. **Are you saying that hypersensitivity reactions aren't treated by premedication? Is that your testimony?**
A. **For Taxotere. There is no prophylactic premedications utilized to prevent hypersensitivity reactions for Taxotere.**
MR. ALY: Can we go back to about about PDX-2-11, please.
BY MR. ALY:
Q. **We're back to the slide which has on it the label, the Hospira label; is that right?**
A. **Correct.**
Q. **That's the same as the Taxotere label; is that correct?**
A. **Correct.**
Q. **Now, that label which is talking about the anaphylaxis, in your proof of infringement you highlighted "rarely fatal anaphylaxis"?**
A. **Correct.**

Q. **Now, the rest of the sentence says, does it not, sir, that that very rarely fatal anaphylaxis has been reported in patients who received the recommended 3-day dexamethazone premedication; is that correct, sir?**

A. **Yes.**

Q. **The label itself is saying even with the dexamethazone premedication, very rarely fatal anaphylaxis still happens, doesn't it?**

A. **Yes.**

Q. **In fact, isn't it true that for Taxol, dexamethazone is used as the premedication?**

A. **For Taxol, dexamethazone is part of the premedication.**

Q. **And for dexamethazone, that is a steroid; right?**

A. **Yes.**

Q. **And dexamethazone was used with Taxotere in the clinical trials; correct?**

A. **It was added midway through the clinical development for the prevention of fluid retention.**

Q. **And as part of the Taxotere clinical trials, the Taxotere ones that Sanofi was responsible for, they tested different combinations of premedications, didn't they?**

A. **Yes.**

Q. **And they evaluated and compared the different kinds of combinations of premedications and applied them to see what happened, what effect they had on hypersensitivity reaction;**

isn't that true?

A. **Correct.**

Q. **Now, for Taxol, you don't know of any comparison of any kinds of premedications that could be used to see that effect on hypersensitivity; right?**

A. **Yes, I do.**

Q. **Now, you don't know about any clinical trials that test what happens with just steroids for Taxol vs. steroids plus antihistamines with Taxol; isn't that true?**

A. **Correct.**

Q. **So you don't know whether or not the antihistamines, when used in combination with Taxol, whether those are required. That hasn't even been tested; right?**

A. **Correct.**

Q. **And, in fact, you know the reason that for Taxol they ended up using three different premedications, that was because it was the same thing that had been done for something else that was causing these kinds of reactions; right?**

A. **Correct.**

Q. **So there was already something established, radio contrast labels. Is that what they were, something like that?**

A. **For patients who had allergic reactions to contrast dye receiving radiologic procedures, if you are allergic to**

the dye, you were treated with antihistamines and steroids.

Q. **So what people knew and was already established by the mid-80s was that there are some dyes that people take and those sometimes cause anaphylactic reactions; right?**

A. **Correct.**

Q. **And what already existed in the prior art, even before the mid '80s was here is some premedication package you can use, it has some steroids, it has some antihistamines; correct?**

A. **Yes.**

Q. **For Taxol, when they started using premedications, they slapped that exact premedication schedule on to Taxol; right?**

A. **Yes.**

Q. **And that worked; right? It reduced the amount and number of hypersensitivity reactions, didn't it?**

A. **Correct. It didn't eliminate them. It reduced them.**

Q. **And to this day, Taxol is still administered to patients to cure cancer; correct?**

A. **Yes.**

Q. **Now, you were here during the opening statements, weren't you?**

A. **Yes, I was.**

Q. **And, counsel, Mr. Pappas described Cremophor being a solution to the problems caused by -- I'm sorry, I reversed**

it. Mr. Pappas was talking about polysorbate 80 being a solution to the problems caused by Cremophor; right?

A. Yes.

Q. And, in fact, the real problem that is out there is the use of a surfactant at all; right? Isn't that true?

A. For? Are we speaking of Taxol?

Q. We're speaking of taxanes generally.

A. For Taxotere, the use of the surfactant polysorbate 80 has been successful. I don't know of an attempt or a need to eradicate polysorbate from the Taxotere formulation.

Q. Isn't there a long standing desire, a long standing need in your community, the medical community to avoid the use of surfactants altogether, if you can?

A. There is a group of researchers who would advocate trying to find, you know, still improved formulations. Sure.

Q. In your expert report, you wrote that the longstanding desire to avoid the use of surfactants entirely, that was in fact a desire; right?

A. Correct.

Q. And the longstanding desire that you're talking about, that is both the polysorbate 80 and Cremophor; right?

A. Correct.

Q. If you could, it would be great to just get rid of any surfactant, wouldn't it?

A. **Correct.**
Q. **In fact, when you talk about other drugs, not the ones we're talking about in today's case but other drugs that don't use steroid premedication, you say that is an advantage; right?**
A. **That's -- I don't know that I would say that. That is a broad range of general statement, when you use prior comparisons of drugs and trials to answer that.**
Q. **Let me ask it this way. When there is a drug that doesn't have either Cremophor or polysorbate 80 -- you have taken the time to point that out, doesn't use either of these surfactants; right?**
A. **Yes.**
Q. **Now, one of the papers you put up by Dr. Weiss was JTX-145. This is that paper, right?**
A. **Yes, it is.**
Q. **And does anywhere in the Weiss article say that a polysorbate 80 surfactant was considered and rejected? You have got it in front of you. I see you looking at it.**
A. **I don't believe so.**
Q. **In fact, polysorbate 80, that wasn't even mentioned in the Weiss article; correct?**
A. **Correct.**
Q. **And does the statement, does the article that we're looking at here in this article, does it tell you that**

another non-ionic surfactant would not work for paclitaxel?

A. **It states that polyethylene glycol was tried as a substitute.**

Q. **Do you know if polyethylene glycol is a surfactant or not a surfactant?**

A. **I'm not a formulator.**

Q. **My question is, does the statements in Weiss that you relied upon, does it tell you that another surfactant would not work for paclitaxel?**

A. **Well, I take the authors at their word. They state that, at present, which was in 1990, there was no suitable substitution for Cremophor EL in the Taxol formulation.**

Q. **And that true, wasn't it? You couldn't buy that in another formulation other than Cremophor; right?**

A. **You couldn't buy Taxol. It was not approved. It was an investigational product at that time.**

Q. **Fine. You couldn't even get Taxol at the time the Weiss article was written in anything other than Cremophor -- correct? -- to administer to a patient?**

A. **You could only administer to a patient at the time of the Weiss article as part of a clinical trial, and so the drug was investigational. And I don't know that there weren't other investigational drugs. There were other investigational trials with paclitaxel, and I don't know if there weren't other attempts at that time.**

Q. **By 1990, do you know of any other formulation of paclitaxel that had been administered in clinical investigations?**

A. **I do not know that, no.**

Q. **The Weiss article doesn't say anywhere that polysorbate 80, another surfactant, wouldn't work, does it?**

A. **It doesn't mention polysorbate 80. It states the no suitable substitute they covered.**

Q. **Now, has Dr. Weiss, to your knowledge, evaluated the difference between Taxotere and Taxol in terms of hypersensitivity reactions?**

A. **I am not aware of such a publication.**

Q. **You have not seen that for this case?**

A. **I have not.**

Q. **I brought this Chemotherapy Source Book, Third Edition. Do you have a chapter in this?**

A. **Yes, I do.**

Q. **And that is by a Michael C. Perry?**

A. **Correct. Mike Perry is the editor.**

Q. **And you contributed a chapter in there?**

A. **I did.**

Q. **And Dr. Weiss contributed a chapter in there?**

A. **He frequently does. I'm not sure of that edition. There have been multiple editions of that book, and I'll take your word that it's listed there.**

Q. **And did you read that Dr. Weiss had reported there is no difference in the formulations and their effects between Taxotere and Taxol?**

A. **I know that Ray has written and lectured on that. I mistook your question. I don't know of a clinical evaluation comparing hypersensitivity reactions between Taxotere and Taxol. Dr. Weiss and others have commented on the relationships, reactions, the premedication.**

Q. **And Dr. Weiss and others have -- I'll get to the other clinical tests we're talking about in a moment. Right now, Dr. Weiss has commented since 1991, since 1990, that when looking at both Taxotere and Taxol, they both have hypersensitivity reactions, right?**

A. **Correct.**

Q. **And that they're equally capable of initiating hypersensitivity reactions; right?**

A. **Of a hypersensitivity reaction, true.**

Q. **Okay. And in 1990, at that time, Taxotere wasn't even yet clinically available at the time Weiss was right; right?**

A. **At the time of this -- he likely wrote this article before that. The clinical trial for Phase I Taxotere began in the summer of 1990.**

Q. **And at the time Weiss wrote that, maybe some time before then, he may not even have known about the Taxotere formulation and product; correct?**

A. **Correct.**

Q. **Now, another article that you rely on is the Van Zuylen paper, PTX-209; isn't that correct?**

A. **Yes.**

Q. **And this Van Zuylen paper, you look to one particular statement within it; right?**

A. **Yes.**

Q. **And that statement appears on Page 10 of this document, doesn't it?**

Eleven. Let's go to 11. So you have got PTX-209 in front of you, Page 11. And that's in the Van Zuylen article you relied on; right?

A. **Right.**

Q. **In the top left paragraph, that's where you were referencing. And if you look at that sentence that says, "notwithstanding these observations;" correct?**

A. **Correct.**

Q. **And those observations referred back to some other predicate facts, didn't they?**

A. **Yes.**

Q. **And if you go to the page before that, on Page 10, and if you go to the bottom right corner, doesn't it say, on the sentence just before the one you were reading, just before the one you were reading that although CrEL -- that is Cremophor EL, right?**

A. **Correct.**

Q. **-- or Tween 80 concentrations have not yet been measured in tumor tissues in any study. Correct?**

A. **Correct.**

Q. **And then it says, it is unlikely that any potential difference in antitumor activity between various formulations is caused by -- it lists these certain specific effects on the top of the page. It says because of their pharmacokinetics selectivity for the blood compartment, correct?**

And it goes on to say, and the undetectable CrEL levels in normal tissue of treated mice, doesn't it?

A. **We skipped an important sentence there.**

Q. **Isn't it true that there were parts of the paragraph you were referring to right before the parts you were quoting? There were, right?**

A. **These words exist before the words I quoted, yes.**

Q. **And you left them off, right?**

A. **I left off these words at the beginning, yes.**

Q. **And when it comes to the sentence you relied upon, you referred to paclitaxel, the drug Taxol, not being effective in tumor models when being given intravenously as a solution in PEG 400 or 10 to 15 percent Tween 80 ethanol; right?**

A. **Yes.**

Q. **And the author here writes, Van Zuylen in 2001, that**

that suggests is that CrEL-based vehicle is essential for in vivo antitumor activity. Right?

A. **Yes.**

Q. **But he is not reaching that conclusion on his own. He cites to this paper 127; right?**

A. **Correct. He is referring to an earlier studies connected by the NCI.**

Q. **And on direct examination, you didn't refer 127; right?**

A. **I did not.**

Q. **So what I want to do is turn to Page 16 of PTX-209.**

A. **Okay.**

Q. **And that is where you find part of the list of references, right?**

A. **Correct.**

MR. PAPPAS: Excuse me, Your Honor. There is a reference to Page 16 but we don't find it. There are pages of the article like 134, 135, and then there is Bates stamps, Hospira, that are in the thousands, but I'm not sure where counsel is reading from.

MR. ALY: Your Honor, when I read a page number, and it's good to clear that up for the record, it's the page number of the document so it can be easily pulled up and relied upon.

The reference number for it is Hospira 0105340.

Do you have that, Mr. Pappas?

MR. PAPPAS: Yes, we do. 340. And for the record, that is Page 140 of the article.

That is what I was getting at, Your Honor. He seems to have page numbers. We can use the page number of the article or the Bates number, either one, but the number he is calling out we don't find anywhere.

MR. ALY: I'll help you out with that. I just wanted to make sure we had it for the graphics as well for today for Your Honor.

THE COURT: You want to have a convention on whether you are going to use Bates or page number.

MR. ALY: I'll refer to the page number.

MR. PAPPAS: Of the article?

MR. ALY: That's correct.

MR. PAPPAS: That's fine.

MR. ALY: And also the page number of the document, but I'll make it clear. Is that all right, Mr. Pappas?

MR. PAPPAS: Your Honor, I don't really care. As long as I know. We have enough numbers.

THE COURT: It's getting late in the day. Why not.

MR. PAPPAS: I want to know where he is.

THE COURT: Okay. So long as you know where we

are.

MR. ALY: Now we know we're on the same page. We're on Page 140 of PTX-209.

BY MR. ALY:

Q. **That's the Van Zuylen article, and that is where they have references listed; correct?**

A. **Correct.**

Q. **And one of these has the number 127; correct?**

A. **Yes.**

Q. **And that 127 is this paper by Rose; correct?**

A. **Correct.**

Q. **Called Taxol, A Review of Its Preclinical in Vivo Antitumor Activity. Right?**

A. **Correct.**

Q. **And that was published in 1992, wasn't it?**

A. **Yes.**

Q. **And 1992 is after the date the patents in this case submitted their French application; right?**

A. **Yes.**

Q. **Let's look at that what that paper says. That's JTX-94.**

JTX-94, that is this paper by Rose, isn't it?

A. **Yes it.**

Q. **It has the title Taxol: A Review of Its Preclinical in Vivo Antitumor Activity. Right?**

A. **Yes.**

Q. **And at the bottom right, that was the one published in 1992 as well; correct?**

A. **Yes.**

Q. **That's the paper cited by Van Zuylen, isn't it?**

A. **Yes.**

Q. **Now, if we go to the seventh page of the document, which is Page 317 of the article, please.**

A. **(Witness complies.)**

Q. **And that has on it a paragraph in the lower left, long paragraph.**

A. **Okay.**

MR. PAPPAS: Your Honor, let me just object. I don't know if he has given the witness a copy of the document.

THE COURT: Does he have a copy?

MR. ALY: Do you have a copy?

THE WITNESS: I do not.

MR. ALY: If you do not, I apologize.

May I approach, Your Honor?

THE COURT: Sure.

(Document passed forward.)

MR. PAPPAS: Do you have a copy for us, Mr. Aly?

MR. ALY: I will hand them out.

MR. PAPPAS: Thank you.

MR. ALY: May I provide a copy for the clerks as well?

THE COURT: Yes.

(Document passed forward.)

BY MR. ALY:

Q. **And you didn't even have the Rose article in front of you today, did you, Dr. Burris?**

A. **Today, I did not. No.**

Q. **And have you seen the paper before?**

A. **Yes.**

Q. **And the lower left paragraph on Page 317, that's what we have here, the first sentence says, that in mice bearing s.c. M109 -- that is one of the experiments in the paper, right?**

A. **Yes.**

Q. **-- IV treatment with Taxol suspended in Tween 80 was not effective. Correct?**

A. **Correct.**

Q. **And that is saying -- so if somebody were just to read that sentence and stop, they might think that Tween 80, that may not work; right?**

A. **Correct.**

Q. **The next sentence says, a completely different outcome was obtained when Taxol was initially solubilized -- that means mixed; right?**

A. **Yes.**

Q. **-- with ethanol plus either Tween 80 or Cremophor. Correct?**

A. **Correct.**

Q. **And we're talking here now about a solution, Taxol dissolved in ethanol plus either Tween 80 or Cremophor; right?**

A. **Correct.**

Q. **Looking at them side by side, aren't we? Isn't that true?**

A. **Yes.**

Q. **And then the next conclusion is a comparison, the next sentence, between these two vehicles was made in an s.c. M109 experiment. Correct?**

A. **Correct.**

Q. **And it goes on to tell you what the different formulations were. Doesn't it?**

A. **Yes.**

Q. **And then the next sentence says, when administered in these formulations, Tween 80 or Cremophor formulation, either one of those, "Taxol achieved similar maximum effects." Correct?**

A. **I apologize. I'm not seeing that. When administered ... okay. I see it.**

Q. **Does it say that?**

A. **Yes.**
Q. **And, in fact, it says using either vehicle; correct?**
A. **Yes.**
Q. **And so that means if you take Taxol and you can put it in either Cremophor or polysorbate 80, it achieved similar maximum effects. Correct?**
A. **Correct.**
Q. **And this is the Rose paper that Van Zuylen was later citing; right?**
A. **Yes.**
Q. **Now, there was another issue that you addressed and that is about the amount of ethanol in the formulations; isn't that right?**
A. **Yes.**

MR. ALY: And if you could please put up PDX-2-13.

BY MR. ALY:

Q. **This was your slide; right?**
A. **Yes.**
Q. **And in this slide, you are showing a few things, starting with the amount of alcohol in a standard drink; right?**
A. **Correct.**
Q. **And that you measured as 17 milliliters; right?**
A. **Correct.**

Q. **You have got amounts of ethanol in the Hospira product; right?**

A. **Yes.**

Q. **And the Apotex product as well; correct?**

A. **Correct.**

Q. **But you don't have the amount of ethanol in the Taxol product, do you?**

A. **Not on that slide, it doesn't.**

MR. ALY: I created one that does. Burris 4. Please show it.

BY MR. ALY:

Q. **Now, this is Burris 4. It's a demonstrative we prepared. It has an added row. You see that row with Taxol there?**

A. **Yes, I do.**

Q. **It has for the amount of ethanol, 26.2 milliliters of ethanol; correct?**

A. **Correct.**

Q. **That's about the amount of ethanol in a Taxol administered dose; correct?**

A. **Correct.**

Q. **Now, compared to the standard drink, wouldn't you agree that is about one and-a-half drinks?**

A. **Yes.**

Q. **And Taxol, as you testified, is administered over**

three hours, right?

A. **Yes.**

Q. **That is about a half drink per hour; right?**

A. **Yes.**

Q. **In the prior art, sometimes people administer Taxol over 24 hours?**

A. **Yes.**

Q. **If they did that, that would be about less than -- it would be a really small number, wouldn't it?**

A. **Yes.**

Q. **Essentially free of ethanol?**

A. **Well, the amount of alcohol in the perfusion will be the same. You just extend it over 24 hours.**

Q. **Okay. So if you take the amount of ethanol and you put it over 24 hours, that is not going to be done in one perfusion day; right?**

A. **If you extend it over -- you would give that infusion in a single bag where it would be hung for 24 hours.**

Q. **And when that was done, alcohol intoxication, that just wasn't seen; right?**

A. **Correct.**

Q. **So it's possible to administer a formulation like Taxol and as a result not get any alcohol intoxication; correct?**

A. **Correct.**

Q. **And Taxol you know has how much ethanol? 50 percent?**
A. **Correct.**
Q. **In fact, with the dose of Taxol products, the Taxotere, when that started Phase I clinical trials, you knew what they used; right?**
A. **Yes.**
Q. **And that used a formulation that had 50 percent ethanol in the stock solution; right?**
A. **Correct.**
Q. **That also didn't cause alcohol intoxication manifestations in patients, did it?**
A. **Correct.**
Q. **Now, you testified a bit also on, another issue I'd like to touch on is your definition of the word "perfusion."**

MR. ALY: Let's take a look at PDX-2-11.

BY MR. ALY:

Q. **And this is referring to the perfusion again; right?**
A. **Yes.**
Q. **And one of the things you did was you looked at what a perfusion means.**

MR. ALY: If we can go back just a bit, sorry, to PDX-2-4.

BY MR. ALY:

Q. **And, Dr. Burris, this is your understanding of what a perfusion means; right?**

A. **Correct.**

Q. **You know now it's no longer an agreed construction; right?**

MR. PAPPAS: Well, objection, Your Honor.

THE WITNESS: I heard that was debatable.

THE COURT: Hold on.

MR. PAPPAS: That is something that counsel discusses with the Court.

THE COURT: Sustained.

BY MR. ALY:

Q. **Do you know whether this construction that you used with the Court is still agreed or not agreed?**

A. **I don't know.**

MR. PAPPAS: Same objection.

BY MR. ALY:

Q. **But it's the one you used; right?**

THE COURT: Yes.

THE WITNESS: This is what I used.

THE COURT: Fine.

BY MR. ALY:

Q. **That's the one you used. And it has in it these words, "suitable for infusion into patients," right?**

A. **Yes.**

Q. **So we started with the word "perfusion," we go to this construction and that has these words "that are included**

suitable for infusion into patients;" right?

A. **Yes.**

Q. **And then from there, you interpret that to require other things about what the perfusion can do; right? Isn't that true?**

A. **Yes.**

Q. **For example, the perfusion has to be reasonably safe; correct?**

A. **Yes.**

Q. **The perfusion has to be stable; right?**

A. **Yes.**

Q. **Perfusion has to be something that is nontoxic; right?**

A. **Correct.**

Q. **And the perfusion has to be something that is effective; right?**

A. **Correct.**

Q. **Now, Taxol, that is a perfusion, isn't it?**

A. **Yes.**

Q. **Taxol sometimes kills people, doesn't it?**

A. **Yes.**

Q. **People die of Taxol. And, in fact, you put up a slide that said sometimes up to 22 percent of patients might die because of Taxol; right?**

A. **I think that number is taken out of context. But the slide said that 22 percent of serious adverse events related**

to hypersensitivity resulted in a death.

MR. ALY: Can we put up, please, PTX-444? Page 133 of the article.

BY MR. ALY:

Q. **And Mr. Pappas had highlighted a paragraph starting with "however" and it ended in "Japan." Do you remember that?**

A. **Yes.**

Q. **And in that paragraph, you relied on this fact, that fatalities occurred in 22 percent of reported cases of hypersensitivity despite the use of premedication prophylaxis; correct?**

A. **Correct.**

Q. **So when you said it was taken out of context, it's not the case that 22 percent of patients get hypersensitivity; right?**

A. **Correct.**

Q. **It's just that when they get a very severe hypersensitivity, then 22 percent of those patients die; right?**

A. **No. This states that 22 percent of the 96 reported cases died.**

Q. **So it's looking at the ones that are reported?**

A. **Right.**

Q. **Of the ones that are reported, 22 percent died, and those were hypersensitivity reaction patients?**

A. **They had severe anaphylaxis.**

Q. **So, Taxol caused severe anaphylaxis?**

A. **Yes.**

Q. **Taxol caused death?**

A. **Yes.**

Q. **Taxol is limited in its amount of stability, isn't it? You can only use it only for a certain amount of time before you have to throw it out?**

A. **Yes.**

Q. **Taxol is not as effective as Taxotere, is it?**

A. **Correct.**

Q. **And Taxol sometimes, no matter how much you give of Taxol, it just doesn't make a difference in the patent; right?**

A. **Correct.**

Q. **Like no matter no matter what, Taxol is called a perfusion, isn't it?**

A. **Yes.**

Q. **And, in fact, even before Taxol was first administered to a patient, when they took the Taxol out of the concentrate and put it into a bag with perfusion fluid, that's what it was called; right? Perfusion fluid?**

A. **Aqueous fluid.**

Q. **Aqueous fluid. And you call it a perfusion bag; right?**

A. **That is called an intravenous bag that is used for giving perfusions.**

Q. **And doctors call that perfusion bags don't they?**

A. **Some probably do. I don't.**

Q. **And when you take the concentrate with Taxol, they put it into that perfusion bag, it was called a perfusion that then was being administered, right?**

A. **Correct.**

MR. ALY: May I have just a moment, Your Honor?

THE COURT: Yes.

(Pause.)

MR. ALY: Thank you, Your Honor. That's all I have.

THE COURT: It's your turn, counsel.

MR. DRESNER: Could we have PDX-2-12, please?

CROSS-EXAMINATION

BY MR. DRESNER:

Q. **So, Dr. Burris, you referred to this slide before as indicating the portion of the Apotex label; correct?**

A. **Correct.**

Q. **And you used this slide to indicate that in your opinion, the Apotex product meets the limitation of having a reasonable expectation of being injected with alcohol causing anaphylactic manifestations; correct?**

A. **Correct.**

Q. **Isn't it true, Dr. Burris, you expressed the opinion that in order for a perfusion to have a reasonable expectation of avoiding such manifestations, you need a sufficiently high ratio of the active ingredient docetaxel to the excipients, to the inactive ingredients, have you not? You have expressed that opinion in your report.**

A. **In my reports, I have, yes.**

Q. **All right. Do you know what is a sufficiently high ratio of docetaxel to the excipients in order to avoid those manifestations?**

A. **I know from my understanding of the Taxotere label and data that that was a successful perfusion, so I based it on that comparison.**

Q. **Okay. So do you know what the ratio is for Taxotere? Did you do that calculation?**

A. **Yes.**

Q. **And do you know what the number is?**

A. **I believe it's listed in my report. I have the .74 milligrams per ML of docetaxel.**

Q. **In fact, during your deposition, didn't you opine that for Taxotere, the ratio was 0.27?**

A. **Yes.**

Q. **Does that refresh your recollection?**

A. **Yes.**

Q. **And do you know that for Taxotere, that ratio is high**

enough to avoid such manifestations?

A. **Yes.**

Q. **And, therefore, is it your conclusion that a ratio higher than that would also avoid such manifestations? Sufficiently high ratio --**

A. **Yes.**

Q. **-- is 0.27. Something higher than that would also achieve the avoidance of the manifestations?**

A. **Yes.**

Q. **How about something lower than that?**

A. **I can't answer that with certainty.**

Q. **In other words, you wouldn't know if something lower than that would be able to avoid those manifestations, would you?**

I'm sorry. You can answer.

A. **No, I guess not.**

Q. **Okay. Have you done the calculation for the Apotex product?**

A. **Yes.**

Q. **And do you know what that number is?**

A. **I would have to refer back to my report.**

Q. **Can I refresh your recollection?**

A. **Sure.**

Q. **At your deposition, you said was 0.17. Do you recall that?**

A. **Yes.**

Q. **That is lower than what it is for Taxotere; isn't that correct?**

A. **Yes.**

Q. **So given it is lower for Taxotere, you really don't know if the Apotex product would avoid these manifestations, do you, based on that arithmetic?**

A. **My conclusion was drawn from the label Apotex provided based on Taxotere.**

Q. **Yes. But when you do the calculation, you have opined that you need a sufficiently high ratio of docetaxel to the excipients in order to be able to avoid these manifestations, and you expressed the opinion that for Taxotere, it's 0.27 and that is sufficiently high; correct?**

A. **And not being -- I did the math within my report, compared to the Taxotere. Not being a formulator, I don't know that I can --**

Q. **So you don't know the answer to that?**

A. **No, I don't.**

MR. DRESNER: Thank you very much.

THE COURT: Thank you, counsel.

Mr. Pappas, you may redirect.

MR. PAPPAS: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. PAPPAS:

Q. **Let me start with where Apotex counsel off. Do you have any reason to believe, based on the label that they have given the Federal Government, that their product will cause severe anaphylactic reaction on a daily or weekly basis?**

A. **No, I do not.**

Q. **And, in fact, what are they telling the world and the Federal Government in the proposed labeling about how they can administer their product or proposed perfusion without causing anaphylactic shock? How often do they say it happens?**

A. **Very rarely.**

Q. **Let me ask you this. Is there anything in the Apotex -- you reviewed the Apotex proposed label; correct?**

A. **Correct.**

Q. **Is there any statement in the Apotex proposed label that says we're different than Taxotere, we don't cause anaphylactic shock?**

A. **No.**

Q. **Is there anything in the Apotex label that says we have a different ratio, we have a lower ratio, so we're going to cause anaphylactic shock?**

A. **No.**

Q. **Is there anything in the Apotex label that puts a physician -- a proposed label -- on notice that they should**

have an expectation that the Apotex label and perfusion will cause anaphylactic shock?

A. **No.**

Q. **Now, let me ask you to look at Plaintiff's Exhibit 553.**

MR. PAPPAS: Mr. Brooks, can we have that up, please?

And, Mr. Brooks, can I have the last page, which is Hospira 43895, please? And highlight the paragraph beginning with the word, "hypersensitivity."

BY MR. PAPPAS:

Q. **Do you see that, Dr. Burris?**

A. **Yes, I do.**

Q. **Now, Mr. Aly asked you a series of questions about the hypersensitivity reactions constituting a severe and unpredictable treatment limiting toxicity for the present Cremophor containing formulation of Taxol given on this schedule.**

Do you see that?

A. **Yes, I do.**

Q. **Let me ask you to review to the prior column.**

MR. PAPPAS: And Mr. Brooks, will you bring up the reference to Patient 3? It starts with the words, "Patient 3 developed hypotension," and go down through the end of that?

BY MR. PAPPAS:

Q. **What is being described there, sir?**

A. **This is a patient who experienced a fatality who passed away as a result of an anaphylaxis to the infusion of Taxol.**

Q. **Based on your reading of this article, do you have an opinion as to whether that is the type of severe and unpredictable treatment limiting toxicity Dr. Kris was referring to by Patient 3?**

A. **Yes, I believe it is.**

Q. **Now, I want to direct your attention to Integrated Safety Summary since Mr. Aly asked you a series of questions about Grade 4 anaphylaxis and premedication. Do you recall those questions?**

A. **Yes, I do.**

Q. **All right. And I believe this is a Joint Trial Exhibit 69. This is the one with all the tablets in it about anaphylaxis.**

A. **Yes, sir.**

Q. **Let's turn to the last page, if you will. And I want to direct your attention to the conclusion of this very voluminous document. And, Mr. Brokes, will you pull up Page SA91770, please?**

Highlight the paragraph that are starts with the words a retrospective analysis and it ends with retention.

First of all, before we go there, where are we in the report? The beginning, middle or the end?

A. **We are in the conclusions.**

Q. **What DO THE AUTHORS routinely do in an INTEGRATED safety summary in the conclusion with respect to all the data that is in there?**

A. **They summarize it into statements that characterize the confidence of the tables.**

Q. **Can you read that for us and tell us what the authors of this integrated summary concluded based on all the data?**

A. **The authors concluded that a retrospective analysis comparing the three main premedication regimens show showed that corticosteroids given orally during at least two days significantly delayed the onset and the severity of fluid retention. No positive impact was found on the incidence of AHSRs, acute hypersensitivity reactions, or of skin toxicity. Antihistamines were found to have a negative impact on the incidence of fluid retention.**

Q. **I want to direct your attention specifically to that third sentence: No positive impact was found on the incidence of AHSR or skin toxicity. On all those tables we with reviewed this morning, where does Grade 4 anaphylaxis come under, under what heading?**

A. **Grade 4 anaphylaxis comes up under the heading of AHSR.**

Q. **What does that stand for?**

A. **Acute hypersensitivity reactions.**

Q. **What are the authors of that entire integrated safety summary saying when they conclude that no positive impact was found on the incidence of AHSR or skin toxicity when they are referring to premedication?**

What are they saying?

A. **They stating that the use of steroids will not influence, decrease the incidence of acute hypersensitivity reactions that are observed.**

Q. **Now, there were some questions to you on cross-examination about the Taxol Phase I trials. Originally, what was the infusion schedule for Taxol?**

A. **Taxol was originally studied as a three-hour infusion once every three weeks.**

Q. **Was it ever attempted as a one hour?**

A. **It had been attempted, a one-hour infusion, several times.**

Q. **By the way, Taxotere is given in one hour. Right?**

A. **Taxotere's approved label is for a one-hour infusion once every three weeks.**

Q. **What happened when they tried to give Taxol in one hour?**

A. **Taxol given over one hour with premedication resulted in what I will call intoxication at our center.**

Q. **Is that a problem that had to be addressed, the alcohol intoxication with Taxol?**

A. **Yes, it did.**

Q. **How did they address it?**

A. **It's been addressed in two different ways: to lengthen the infusion or and to reduce the dose, the amount of drug that was administered over one hour.**

Q. **Were either of those actions, did they have to be taken with Taxotere?**

A. **No.**

Q. **And could Taxotere be administered without alcohol intoxication even within one hour?**

A. **Yes.**

Q. **Let me ask you to direct your attention to Joint Trial Exhibit 145. Specifically, Mr. Brooks, can you bring up the quote that we have focused on previously that starts at the bottom of Page 44784 and goes to 44785.**

This is the paragraph we covered before where Dr. Weiss and his authors conclude at present there is no suitable substitute for Cremophor EL in a Taxol formulation.

Do you see that?

A. **Yes, I do.**

Q. **You were asked about that by Mr. Aly. Correct?**

A. **Yes, I was.**

Q. **What does he recite specifically that was tried as a**

substitute?

A. **He states that polyethylene glycol has been tried as a substitute, but this chemical appeared to decrease the antitumor activity of Taxol in murine tumor studies.**

Q. **Now, Mr. Aly asked you about whether or not polysorbate 80 was expressly mentioned. Do you see that?**

A. **Yes.**

Q. **Do you remember that?**

A. **I do recall that.**

Q. **My question is, at this time that Dr. Weiss wrote this article in 1990, was polysorbate 80 approved by the FDA?**

A. **Yes, it was.**

Q. **Was it known about by physicians generally?**

A. **Yes.**

Q. **Had it been used in the early eighties in an etoposide formulation for cancer?**

A. **Yes, it had been.**

Q. **Can you think of any reason, any reason, Dr. Burris, why so distinguished a gentleman as Dr. Weiss and Dr. Von Hoff and the rest of them would have written, At present there is no suitable substitute for Cremophor in Taxol formulations if polysorbate 80 was a suitable substitute? Can you give us any reason for why they would have written that?**

A. **No, I cannot.**

Q. **Can I ask you to direct your attention to Plaintiffs' Trial Exhibit 209. This is one of the Dr. Sparreboom's articles, Hospira's consultant?**

I want to direct your attention to Hospira 105335.

MR. PAPPAS: Mr. Brooks, if you could bring that page up.

BY MR. PAPPAS:

Q. **It's also Page 135 in the top right-hand corner.**

The you can start on 105334 with the language Mr. Aly read the witness, although CrEL or Tween concentrations, start there at the bottom, and then go through the antitumor activity.

Highlight that, please.

Now, Dr. Burris, put this all together. Mr. Aly asked, read you, had you read the language that started Although CrEL, which is Cremophor, or Tween 80, concentrations have not been measured and so on, and I had to read earlier in your direct the notwithstanding language. All right?

A. **Yes.**

Q. **Read that together, not out loud, and what is the author telling us after the Cremophor reference that Mr. Aly read to you when he said notwithstanding these observations? What is that a reference to? What observations?**

A. **It is a reference to the sentences above that that stated that the Cremophor, the various formulations had no direct cytotoxic effects or cell cycle arrest by the surfactants.**

Q. **Now, there is a cite or a footnote to 127 which Mr. Aly pointed out to you is the Rose article. Correct?**

A. **Correct.**

Q. **Without rehashing the Rose article, and Mr. Aly's interpretation of it, what was Dr. Sparreboom's, or their consultant's, interpretation of that article? What did he write this?**

A. **His interpretation of that article and the results contained within were that paclitaxel was not effective in tumor models when it was given intravenously as a solution with either a polyethylene glycol 400 or polysorbate 80. And he interpreted that the Cremophor EL based vehicle was essential for in vivo antitumor activity.**

Q. **Do you have an opinion as to whether that was the commonly held belief at that time?**

A. **That was the commonly held believe at that time.**

Q. **Aside from the debate Mr. Aly and I have about the Rose article, I am not sure we will ever resolve that, the question I have for you in this lawsuit, though, the article, the statement by Dr. Sparreboom, do you have an opinion if this is an indication of how skilled artisans**

reading that article would have interpreted it, in other words, that Cremophor was essential for antitumor activity?

MR. ALY: Objection, Your Honor. Foundation of skilled artisans. Not this witness's area of expertise.

MR. PAPPAS: I will amendment the question, Your Honor.

BY MR. PAPPAS:

Q. **Do you have an opinion as to how oncologists in the field would have understood Dr. Sparreboom's statement here?**

A. **Yes. This article is published almost ten years after the Rose article. During that time period, myself and other medical oncologists were taught, lectured to, and referenced research information which suggested that Cremophor was needed for Taxol and was essential for its antitumor activity.**

MR. PAPPAS: Might I have a moment, Your Honor?

THE COURT: Yes.

(Pause.)

MR. PAPPAS: Your Honor, I assume we have reached the end of the day. I have finished my redirect.

THE COURT: We will adjourn for the day.

(Court recessed at 4:34 p.m.)

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